

# Supporting Information Appendix

## Metagenomic Systems Biology of the Human Gut Microbiome Reveals Topological Shifts Associated with Obesity and IBD Sharon Greenblum, Peter J. Turnbaugh, and Elhanan Borenstein

### Table of Contents

Supporting Text .....	1
Datasets: .....	1
Analysis of Data from Turnbaugh et al: .....	1
Communities as Supra-organisms: .....	2
Choice of Enrichment Metric: .....	2
Sensitivity of Results to Missing or Erroneous Annotation Data: .....	2
Alternative Enrichment Metrics: .....	3
Analysis of Non Transport-Related Enzymes: .....	3
Robustness to Noise in Read Count Data: .....	3
Robustness to Alternative Network Construction Methods: .....	4
Seed Set Analysis: .....	5
Functional Annotation and Functional Enrichment Analysis: .....	5
Single Genome Analysis: .....	6
Topology-Based Biomarker Analysis: .....	6
Significance Analysis of Observed Differences in Global Network Properties: .....	6
References .....	7
Supporting Figures .....	8
Supporting Tables .....	19

### Supporting Text

#### **Datasets:**

For the fecal microbiomes from unrelated individuals, metagenomic shotgun sequencing reads, predicted genes from the assembled scaffolds, and KEGG annotations (1) were downloaded from [http://www.bork.embl.de/~arumugam/Qin\\_et\\_al\\_2010/](http://www.bork.embl.de/~arumugam/Qin_et_al_2010/) (2). In order to obtain abundance information, the sequencing reads from each sample were mapped onto the non-redundant gene catalog with SSAHA2 (parameters: -output cigar -score 20 -best 1 -solexa -kmer 12 -skip 12) (3). Metagenomic shotgun sequencing reads from a smaller set of twin-mother trios (4) were re-analyzed separately, including samples from 9 lean/overweight and 9 obese individuals. All sequences were mapped onto the KEGG database version 52 (BLASTX e-value<10<sup>-5</sup>, %identity>50, score>50) (see (4) for a detailed discussion of the parameters used). Sequences were annotated with all KOs (KEGG orthologous groups) of the top KO-associated match among the top 100 matches. Sequences with multiple top KO-associated matches with the same e-value were annotated with the union set of KOs. Following the rationale of (2), we imposed a threshold of 2 reads to allow the inclusion of rare genes; all KO abundances below this threshold were set to zero. For both datasets, counts were normalized within each sample to represent the relative abundance of each enzyme (KO) in each sample, thereby accounting for differences in sampling depth. Mean normalized enzyme counts across the two datasets were significantly correlated (R=0.86; Spearman correlation test).

#### **Analysis of Data from Turnbaugh et al:**

In addition to the analysis of the 124 deeply sequenced microbiomes (2), we performed a similar analysis of 18 microbiomes from mother-twin trios characterized as lean/overweight (n=9) or obese (n=9) (4). Of the 1195 enzymes in the community-level network constructed from these microbiomes, 120 were enriched in obese microbiomes (odds ratio>2) and 177 were depleted (odds ratio<0.5). 1159 (97%) of the enzymes were also present in the network constructed from the 124 samples of (2). Tests of association (Table S3) between differential abundance score and network topology revealed

that differential abundance was negatively correlated with centrality ( $p < 9.7 \times 10^{-8}$ ; Spearman correlation test). The centrality scores of obesity-associated enzymes in this dataset are significantly lower than the centrality scores of enzymes not associated with obesity ( $p < 0.0002$ ; Wilcoxon rank-sum test;  $p < 0.04$  and  $p < 0.0006$  respectively when considering obesity-enriched and obesity-depleted enzymes separately). These enzymes are significantly over-represented in the peripheral tier of the network ( $p < 0.0012$ ; Hypergeometric test): 30.4%, 24.8%, and 19.3% of the enzymes in the peripheral, intermediate and central tiers respectively are associated with obesity.

### ***Communities as Supra-organisms:***

Microbial communities have often been described as supra-organisms, ignoring the individual species comprising each community, and treating the community as a single adaptive organism that functions in a given environment. While there are several reasons to assume that for a large scale analysis the partition of a metabolic pathway among the various species and the compartmentalization of metabolic processes can be ignored, this assumption is often the outcome of necessity; reliable methods for decomposing complex metagenomic samples into species-specific data are currently lacking. Comparative metagenomic analysis, by definition, takes a similar view, assuming that the set of genes found in a metagenome reflects community-level metabolic capacity. In this study, we extend this approach, putting microbial communities on an equal footing with single species and treating the entire community as a single, independent biological system (5). This approach allows us to ask questions about the organization of the community, its function, and its interaction with the host, and to address these questions using *in silico* modeling techniques and systems-level methods originally developed for studying single organisms. Specifically, we can project variation in gene content onto a community-level metabolic network and identify systems-level variations that cannot be revealed with traditional comparative analysis.

### ***Choice of Enrichment Metric:***

The selection of a suitable measure of gene or pathway enrichment is a non-trivial component of comparative metagenomic analyses, since statistical results can be heavily influenced by missing data, sample size, data magnitude, normalization technique, or assumptions about the distribution of values. Following the example of recent metagenomic studies (4, 6, 7) we chose the odds ratio as the most appropriate measure of enzyme enrichment. The odds ratio measure has a number of important benefits. It has a straightforward *interpretation*, conveying the likelihood of observing a given enzyme in the sample set relative to a comparison data set. It provides a *continuous, unit-free* measure of comparative abundance, without assuming any specific *distribution* or *scale* within the data values. This is especially important when assessing hundreds to thousands of enzymes, each with a considerably different range of expected abundances. See also “*Alternative Enrichment Metrics*” below.

### ***Sensitivity of Results to Missing or Erroneous Annotation Data:***

We examined the effect of missing or erroneous metabolic annotation data on the calculated centrality scores and on the observed correlation between centrality and differential abundance in obesity using a simulation analysis. Specifically, we considered the available metabolic annotations from the entire KEGG database as a reference “complete” dataset and examined the effect of either deleting a varying fraction of all enzymatic annotations in this dataset or rewiring some of the derived links between enzymes. For each deletion level we generated 100 perturbed datasets (i.e., a dataset in which a given percentage of all enzymatic annotations are deleted at random), used these perturbed datasets to construct metabolic networks, and examined the centrality scores and centrality-related results in these networks. As metabolic network construction that is based on as low as 50% gene coverage may still detect 70% of network reactions (8), we analyzed the effect of deleting up to 30% of the enzymatic annotations included in KEGG.

We first examined the effect of such deletions on the calculated centrality values used in our analysis. As is evident from Fig. S4, the centrality values of the remaining enzymes are hardly affected, even when 30% of the annotations in the KEGG database are deleted. More importantly, as our analysis concerns the relative centrality of the various enzymes (rather than their absolute values), we find that the centrality values obtained for the perturbed datasets are markedly correlated with the centrality values in the original full dataset ( $R = 0.998, 0.996, 0.984$ , and  $0.97$  after deleting 5%, 10%, 20%, and 30% of the annotations respectively; Spearman correlation test,  $p < 10^{-324}$  in all cases). Rewiring 10% of the links between enzymes (to simulate erroneous annotations) similarly yields highly correlated centrality values ( $R = 0.79$ ,  $p < 10^{-324}$ ).

We additionally checked whether the correlation between centrality and obesity-associated differential abundance that was observed in the complete KEGG-based network still holds in the perturbed, incomplete networks. We found that in *all* 100 networks based on either 5%, 10% and 20% deleted annotations and in 98 of the 100 networks based on 30% deleted annotations, this correlation analysis still yields a significant result. Figs. S5A-B further demonstrate the relatively

little effect incomplete annotation may have on the markedly different centrality scores of obesity-associated vs. non-associated enzymes and on the over-representation of obesity-associated enzymes in the periphery of the network. Similarly, all 100 perturbed networks in which 10% of the links were rewired exhibit a significant correlation between centrality and obesity-associated differential abundance.

### **Alternative Enrichment Metrics:**

While we believe that the odds ratio test is the most appropriate metric for our data (as described above, in the section “Choice of Enrichment Metric”), we confirmed that our main results are not an artifact of the odds ratio metric specifically and that these results hold under several alternative strategies for identifying enzymes associated with a given host state. These strategies intended to capture various aspects of the possible association between enzyme abundances and the state of the host.

First, we examined the effect of augmenting the odds ratio criterion with statistical tests aimed at identifying enzymes with a consistently different abundance profile between the two host states (e.g., obese vs. lean). One such test is based on shuffling the sample labels and is described in more detail in the section “Robustness to Noise in Read Count Data” below. In a second test, we alternatively used a Wilcoxon rank-sum test to further limit enzymes that appear to be enriched or depleted according to the odds-ratio test to those that exhibit a significantly ( $p < 0.05$ ) different set of abundances values in obese or IBD according to the ranksum test.

Second, we used a fundamentally different test, based solely on the presence or absence of enzymes in the various samples rather than on their abundances. Specifically, we identified enzymes that are present in a significantly high or a significantly low number of samples from a given host state considering the total number of samples in which they are present. A Hypergeometric test was used to calculate over- or under-representation with a threshold of  $p < 0.05$ .

Next, we used a test based on the *difference* in enzyme abundance, rather than on the ratio. In order to avoid biasing this measure toward the most abundant enzymes overall, we first mapped enzyme abundances to a uniform distribution by ranking the enzymes within each sample from most abundant to least abundant. We then measured the difference between the mean rank of each enzyme in obese samples and its mean rank in lean-healthy samples. Since no clear or intuitive threshold (analogous to the two-fold threshold commonly used in the odds-ratio test) exists for rank difference, here we defined the enzymes with the 10% highest calculated differences and the 10% lowest differences as enriched and depleted enzymes respectively.

Finally, we examined the divergence in the overall distribution of enzyme abundance between the two host states. To this end, we use the Jensen–Shannon divergence measure to quantify the similarity between the distributions of abundance values of a given enzymes in obese vs. lean samples. We again used rank-normalized enzyme abundances to avoid bias. We then bin the rank values associated with each enzyme across the various samples to obtain a distribution profile. Since Jensen–Shannon divergence provides an absolute (rather than signed) measure and does not separate enriched from depleted enzymes, here we defined all enzymes with the 20% most divergent distributions as obesity-associated (using only the 10% most divergent enzymes did not qualitatively change the results).

We find that applying any of these metrics to identify enzymes associated with obesity does not qualitatively change the patterns reported in the main text. Specifically, the strong link between obesity-associated enzymes and centrality is still observed under all these metrics. The pertaining p-values and additional details can be found in Table S3.

### **Analysis of Non Transport-Related Enzymes:**

As transport enzymes are likely to be found at the periphery of the network, we further validated that the correlation between differential abundance and centrality is not a product of the over-representation of transport enzymes in obese microbiomes. Omitting all enzymes annotated with a transport-related function (i.e., KEGG BRITE classes ‘Membrane Transport’ and ‘Transport and Catabolism’) and repeating the analysis outlined above, we found that the differential abundance score of the remaining enzymes is still negatively correlated with their centrality ( $R = -0.16$ ,  $p < 6.6 \times 10^{-10}$  [obesity];  $R = -0.14$ ,  $p < 2.8 \times 10^{-8}$  [IBD]; Spearman correlation test). Similarly, the centrality of non-transport-related obesity-associated enzymes is significantly lower than centrality scores of enzymes not associated with obesity ( $p < 1.6 \times 10^{-5}$  [obesity];  $p < 3.2 \times 10^{-5}$  [IBD]; Wilcoxon rank-sum test) and such non-transport obesity-associated enzymes are significantly over-represented in the peripheral tier of the network ( $p < 3.1 \times 10^{-5}$  [obesity];  $p < 1.7 \times 10^{-4}$  [IBD]; Hypergeometric enrichment test).

### **Robustness to Noise in Read Count Data:**

Clearly, shotgun metagenomic data is extremely noisy and often represents only a sparse sample of the genomic material found in the microbiome. This noise induces a non-negligible level of inaccuracy in read count and gene abundance data,

and consequently in our differential abundance estimates. Such inaccuracies are especially severe in genes with an overall low abundance where, for example, a two-fold difference (e.g., from 1 to 2 reads) most probably represents a sampling error rather than a real signal of association with a given host state.

To confirm that the findings presented in the main text are not an artifact stemming from such low count or noisy data, we used two assays. First we confirmed that the link between obesity-associated or IBD-associated enzymes and centrality holds when the analysis is limited to enzymes with a substantial read count. The analysis presented in the main text follows the rationale presented in (2) and imposes a threshold of 2 reads (see also the “Datasets” section above). Here, we further validated that using a threshold of 5, 25, or 50 reads does not qualitatively affect the results reported in the main text. Specifically, using any of these threshold values, we found that differential abundance scores are still negatively correlated with centrality, centrality scores of obesity- or IBD-associated enzymes are significantly lower than centrality scores of non-associated enzymes, and these enzymes are significantly over-represented in the peripheral tier of the network (see Table S3 for details and p-values).

Second, we applied a measure of significance to our odds ratio score by shuffling the sample labels 1,000 times and recalculating the odds ratio of each enzyme using these shuffled datasets. A p-value was assigned to each enzyme representing the fraction of times an odds ratio more extreme than the real value was obtained. Enzymes with low p-values therefore represent enzymes that are *consistently* enriched or depleted in obese or IBD samples and are more likely to capture genuine association with the host state. In contrast, enzymes that appear to be differentially abundant only due to a few exceptionally high (or low) counts in some samples (e.g., due to noise) will fail such a test. We classified enzymes with an odds ratio >2 and a p-value < 0.05 as *consistently enriched*, and enzymes with an odds ratio <0.5 and a p-value < 0.05 as *consistently depleted*. Repeating our analysis using this more stringent criterion for association with obesity or IBD still demonstrated a significant correlation between such consistently associated enzymes and centrality (see Table S3 and main text).

Finally, it should also be noted that the correlation between centrality and differential abundance scores was observed in two independent datasets: An Illumina-derived data from 124 individuals and a 454 FLX-derived data from 18 individuals (see Table S3). These two datasets represents fundamentally different metagenomic technologies and different noise profiles.

### **Robustness to Alternative Network Construction Methods:**

The construction of a network that accurately depicts the relationships between metabolic enzymes operating in the gut microbiome is central to our analysis. The network generated based on the metagenome content represents our best available approximation of the gut microbiome metabolism and we therefore base our analysis in the main text on this network. However, this network is clearly limited by sampling depth and detectable enzymes and may accordingly be incomplete and inaccurate. Moreover, the network construction strategy and the specific annotation framework used may further affect the topology of the resulting network. We therefore validate here that our findings are not an artifact of the specific network construction method or annotation system. To this end, we generated networks using a number of alternative strategies and examine the link between host-associated enzymes and topology in these alternative networks.

We first constructed networks based on extensions or modifications of the KEGG-based enzyme annotation. The first of these networks was constructed from all enzymes in the KEGG database rather than the subset of enzymes found in the metagenome data. This network accounts for enzymes that do not appear in our data-derived network due to sampling bias or low abundance. A second alternative network was constructed by omitting currency metabolites from the network wiring scheme. Currency metabolites (such as ATP or H<sub>2</sub>O) are those metabolites which are common to a very large number of reactions and could therefore induce overly-dense clusters of connected enzymes with limited biological meaning. The omission of such metabolites is a common practice in the construction of many metabolite-based networks (9). We compiled a list of currency metabolites (including ATP, ADP, CO<sub>2</sub>, H<sup>+</sup>, H<sub>2</sub>, H<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, H<sub>2</sub>O<sub>2</sub>, H<sub>2</sub>S, NAD<sup>+</sup>, NADH, NH<sub>3</sub>, Nitrate, Nitric oxide, Nitrite, O<sub>2</sub>, Phosphate, Pyrophosphate, Sulfate, and Sulfite) from a search of relevant literature (9-11) and constructed a network in which these metabolites were ignored when generating edges.

We next examined the effect of reaction directionality. In the main analysis we treat links between enzymes as directed edges, in which an input enzyme catalyzes a reaction producing a metabolite that an output enzyme uses as a substrate. In reality however, the direction of metabolic flux through specific enzymes is often variable, and may be dependent on a number of factors such as metabolite concentration or other environmental conditions. Thus, we constructed an alternative network in which all edges were considered undirected.

Finally, while the use of KEGG has become widespread as a comprehensive and accurate source of metabolic functional information, other databases (e.g. SEED (12)) provide alternative versions of enzyme annotations and their associated reactions. To demonstrate that our results are independent of the KEGG metabolic database altogether, we

constructed an alternative network, based exclusively on annotations and reaction data from the SEED annotation system and the MG-RAST analysis server (13). Specifically, SEED-based enzyme annotations for reads found in the metagenomes of the 124 unrelated individuals were downloaded from MG-RAST (<http://metagenomics.anl.gov/metagenomics.cgi?page=DownloadMetagenome&metagenome=4448044.3>), resulting in 1296 unique enzyme annotations. An odds ratio was calculated for each enzyme based on the pooled count of annotated reads in lean vs. obese samples. Metabolic reactions associated with each enzyme (using their EC number) were downloaded from the modelSEED (14), a tool designed to generate automated genome-scale metabolic models (<http://seed-viewer.theseed.org/ModelSEEDdownload.cgi?biochemCompounds=1>). As MG-RAST does not currently connect directly to the modelSEED framework, we used this modelSEED reaction data to directly generate a metabolic network of 1,005 connected enzymes and projected MG-RAST based odds ratio scores onto this modelSEED based network. For this analysis, information regarding the cellular location and conformation of various reactions was ignored. Currency metabolites were excluded as described above. Due to the high density of the SEED-based network, an additional set of currency metabolites (NADP, NADPH, CoA, UDP, SAM, AMP, S-Adenosylhomocysteine) was excluded by identifying the top 0.1% of metabolites according to their frequency in all enzyme-associated metabolic reactions.

We find that all four of these alternative networks support our results regarding the relationship between obesity-associated enzymes and centrality (Table S3). Specifically, in each network, we find that obesity-associated differential abundance scores are negatively correlated with enzyme centrality, and that obesity-associated enzymes have lower centrality than other enzymes and are over-represented in the peripheral tier (Table S3).

As further validation of our results, we examined a null version of the network in which edges were randomly rewired (while preserving the in- and out-degree of each node) according to the algorithm outlined in (15). In contrast to the patterns observed in the real network, we find that of 100 versions of this randomized network, none demonstrated the same low centrality of obesity-associated enzymes, nor the over-representation of obesity-associated enzymes in the peripheral tier. This suggests that the relationship between obesity-associated enzymes and centrality is dependent on the specific network structure dictated by metabolic interactions within the human metagenome.

### **Seed Set Analysis:**

The metabolic seeds of the network were determined computationally according to the framework outlined in (16). This framework uses a novel graph-theory based algorithm to analyze the topology of metabolic networks and to infer the set of compounds that are exogenously acquired. This set (termed 'seed set') reflects the metabolic interface between the organism and its surroundings, approximating its environment. Applying this algorithm to the metabolic networks of hundreds of species, this framework was used to generate a large-scale dataset of predicted environments. Seed sets were shown to successfully characterize the biochemical environment of microbial species and to correlate with several basic properties characterizing their environments. Previous studies further used this framework to identify universal patterns of adaptation of organisms to their niches (16), to predict interactions between microbial species and their hosts (17), and to quantitatively characterize ecological strategies across a large array of microbial species (18). While the seed algorithm was designed initially to analyze metabolite-based networks, here we use it to determine the seeds in enzyme-based networks. Identified seeds therefore represent enzymes operating on exogenously acquired compounds (rather than the exogenously acquired compounds themselves).

Over- or under-representation of seeds among the various enzyme sets (e.g. obesity-associated enzymes) was determined using a hypergeometric enrichment test. Specifically, for each such set, a p-value was assigned based on the calculated probability of observing  $S$  or more seeds in a random set of  $N$  enzymes, given the number of seeds in the entire network. Here,  $N$  is the total number of enzymes in the set and  $S$  is the number of enzymes in this set identified as seeds. Over-representation of seeds among the 350 obesity-associated enzymes was further validated by assessing the number of seeds in 10,000 randomly selected sets of 350 enzymes ( $p < 2 \times 10^{-4}$ ).

### **Functional Annotation and Functional Enrichment Analysis:**

The KEGG BRITE database was mined to annotate each enzyme with zero or more functional categories. A Hypergeometric enrichment test was used to assess the over- or under-representation of each functional category within the set of enriched or depleted enzymes (Table S4). P-values were obtained for each function independently by calculating the probability of observing  $S$  or more (for over-representation analysis) enzymes annotated with a given function in a random set of  $N$  enzymes, given the frequency of that functional annotation in the entire network. Here,  $S$  refers to the number of enzymes annotated with this function within a given set of enzymes (e.g., obesity-enriched enzymes) and  $N$  refers to the total number of enzymes in this set. Both over- and under-representation of functional annotations were considered.

### ***Single Genome Analysis:***

The reference genomes of 326 human-associated microbial species were downloaded from the Integrated Microbial Genomes (IMG) Database (19) by searching for species labeled as being part of the Human Gut Microbiome Initiative or the Human Microbiome Project (Table S5). These genomes were annotated with KEGG orthologous groups and the number of associated genomes was recorded for each enzyme within our network. Correlations were then assessed between enzyme centrality or differential abundance and prevalence within this set of genomes. The reference genome prevalence of the 350 obesity-associated enzymes was further compared to the mean genome prevalence of 10,000 randomly selected sets of 350 enzymes ( $p < 10^{-4}$ ).

### ***Topology-Based Biomarker Analysis:***

In addition to enhancing the digestion of complex carbohydrates and proteins, the gut microbiome encodes a diverse set of genes for xenobiotic metabolism (6) influencing the bioavailability, toxicity, and activity of therapeutic drugs and dietary supplements (e.g. (20)). Interestingly, both the obesity- and IBD-associated gene sets with distinct topological features (Tables S2A-D) encode enzymes for xenobiotic metabolism, most notably those for the metabolism of choline and p-cresol (enriched and depleted in IBD/obesity respectively). Recent work has linked microbial metabolism of choline to cardiovascular disease (21), while p-cresol produced by the gut microbiome may interfere with the sulfonation of acetaminophen (22). Follow-up studies specifically targetted at links between xenobiotic metabolism, obesity, and IBD will be necessary to confirm these associations and to determine if they contribute to disease.

### ***Significance Analysis of Observed Differences in Global Network Properties:***

In the main text we demonstrated that the network that represents obese samples is less modular than the network that represents lean samples. Here, we confirm that this result is significant and is not expected at random from multiple individual realizations of networks with similar topological properties. To this end, we randomly shuffled the host state labels (e.g., lean vs. obese) 1,000 times, constructed lean- and obese-specific networks based on these shuffled sample labels, and used these networks to generate a null distribution of modularity scores expected for a random set of samples. We compared the modularity scores obtained for the real lean and obese networks to modularity scores obtained with the shuffled sample labels. We find that the difference between the modularity scores of our real lean- and real obese-specific networks is significantly greater than the pairwise differences of shuffled lean- and obese-specific networks ( $p < 0.027$ ; Fig. 3B). Interestingly, when examining the modularity of lean- and obese-specific networks separately, we find that while the modularity of the real obese-specific network is significantly lower than the modularity of the shuffled-obese networks ( $p < 0.05$ ), the modularity of the lean-specific network is higher than most (83%) shuffled-lean networks but is not significantly different (Fig. S9A-B). This suggests that the observed difference in the modularity between lean- and obese-specific networks can be attributed mostly to obese samples which deviate from the 'normal' network topology.

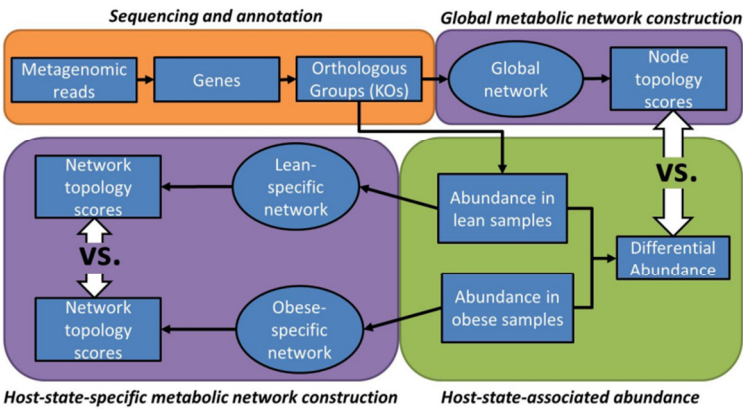
We further confirmed the significance of the reported difference in modularity between lean- and obese-specific networks using an alternative null distribution generated by shuffling network edges, as described in (15) and in the section "*Robustness to Alternative Network Construction Methods*" above. For each iteration, network edges in the microbiome-wide network (composed of enzymes found in the union of all samples) were randomly shuffled, and sub-networks were extracted, each representing the set of enzymes found in samples from a specific host state. In total, 1,000 pairs of these shuffled lean- and obese-specific networks were generated. For both obese-specific and lean-healthy-specific networks, the shuffled networks are significantly less modular than the real network. Yet, the observed *difference* in modularity between the true lean- and obese-specific networks is significantly greater than the modularity differences obtained from the shuffled networks ( $p < 2.0 \times 10^{-3}$ ; Fig. S10).

Other topological features that seem to differ (though not as strongly as the difference in modularity) between host state-specific networks are further illustrated in Fig. S11A-D. Specifically, the density of IBD-specific networks appears to be higher than the density of lean-healthy networks, though not significantly so (Figs. S11A, S11C). We also find that the node count of the obese-specific network is significantly lower than the node count of lean-specific networks ( $p < 0.001$ ; Fig. S11D).

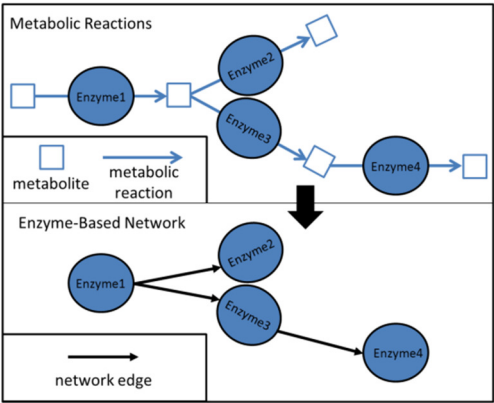
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**A**



**B**



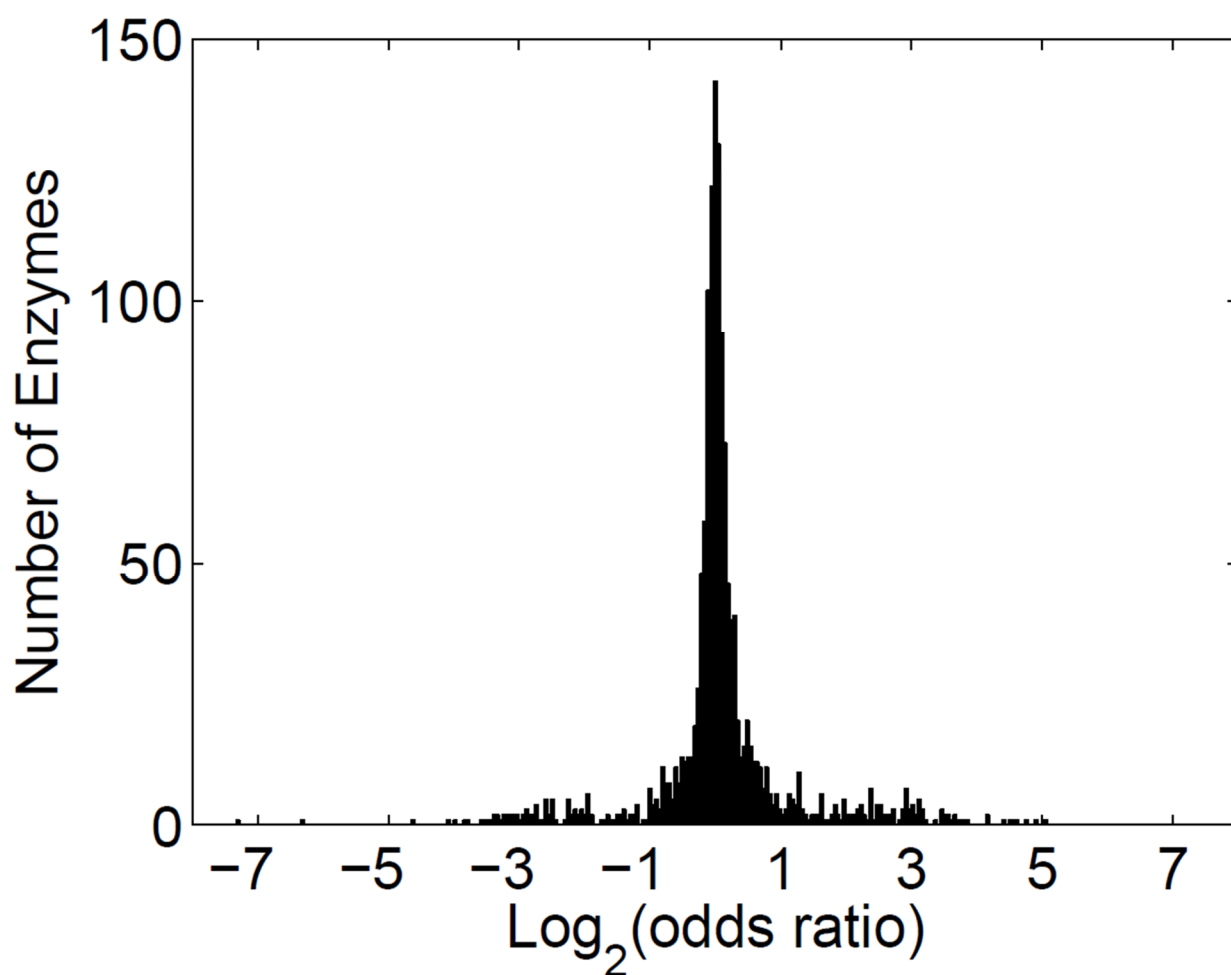
364  
365 **Fig. S1.** Network-based analysis of community metabolism. **(A)** A flowchart of the analysis presented in this  
366 study. Briefly, metagenomic reads from various samples are mapped to orthologous groups (KOs). The  
367 differential abundance score of each enzyme (KO) is calculated by comparing the enzyme abundance in samples  
368 from different host-states. A global metabolic network is constructed from the entire sample-wide set of  
369 enzymes, as depicted in **(B)**. Each enzyme is assigned a set of substrate and product metabolites (white squares)  
370 according to the reactions catalyzed by the enzyme as annotated in KEGG. A search is performed to identify all  
371 enzyme pairs in which a product metabolite of one enzyme is a substrate metabolite of the other. Directed  
372 network edges are then drawn between each identified enzyme pair. Once the network has been generation,  
373 topological features of individual enzyme nodes are compared to the enzyme's differential abundance. A  
374 parallel analysis involves the construction of a separate network from enzymes found in the subset of samples  
375 from a specific host state. Network-wide topological features are compared across these host-state-specific  
376 networks.



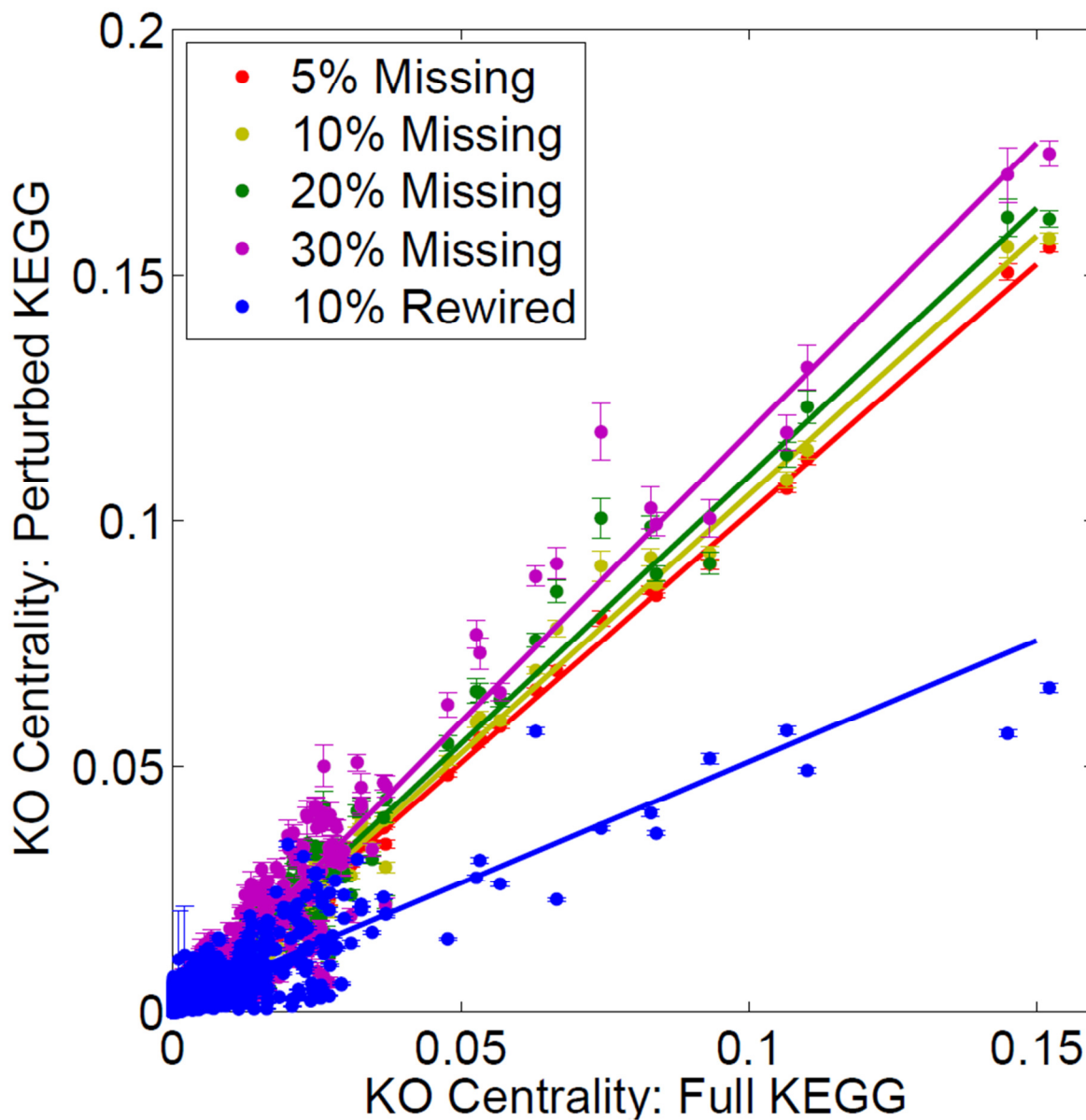
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graph LR
    A((A)) --> B((B))
    B((B)) --> D((D))
    C((C)) --> E((E))
    D((D)) --> F((F))
    D((D)) --> E((E))
    E((E)) --> F((F))
    E((E)) --> H((H))
    F((F)) --> I((I))
    F((F)) --> G((G))
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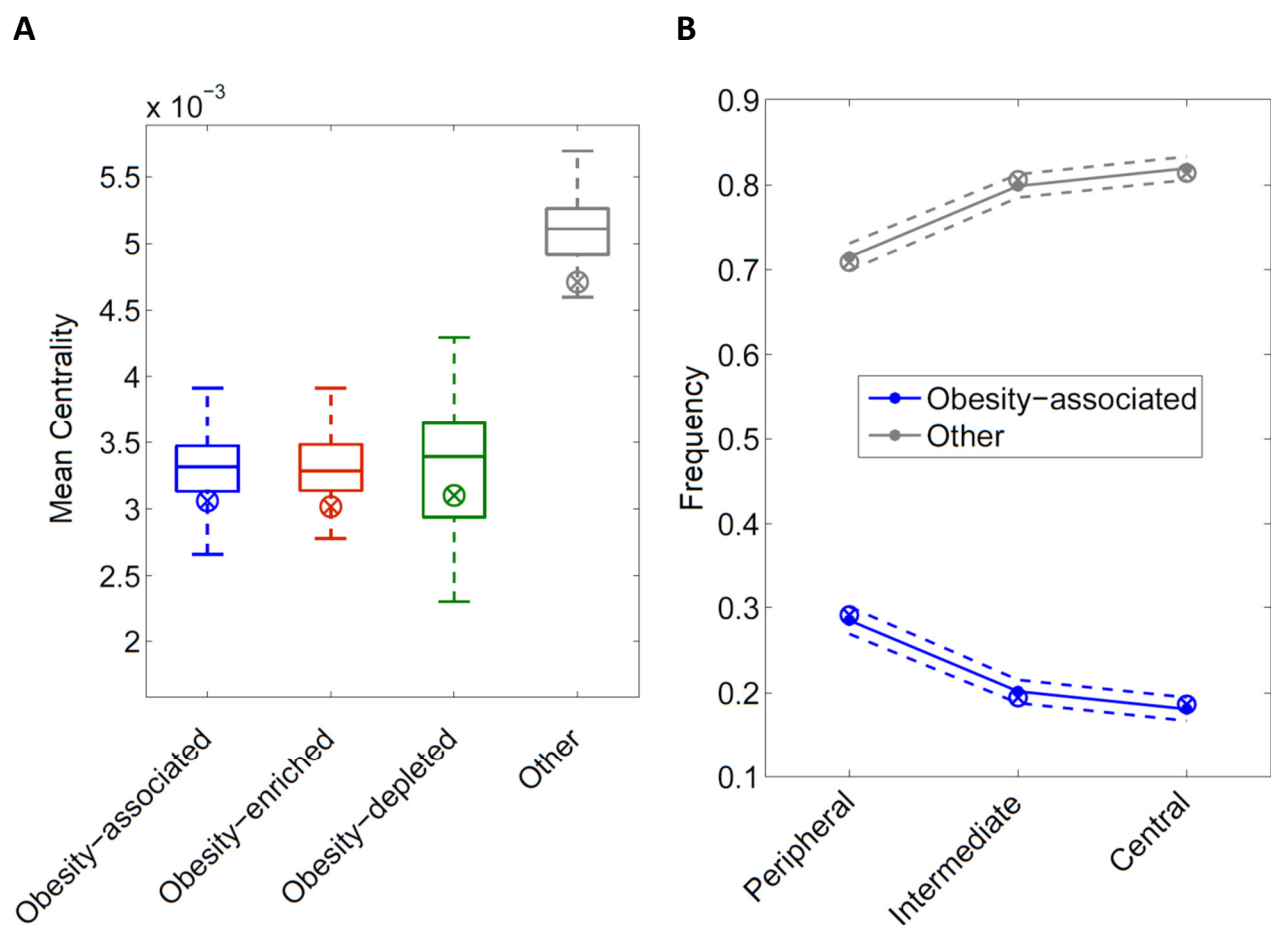
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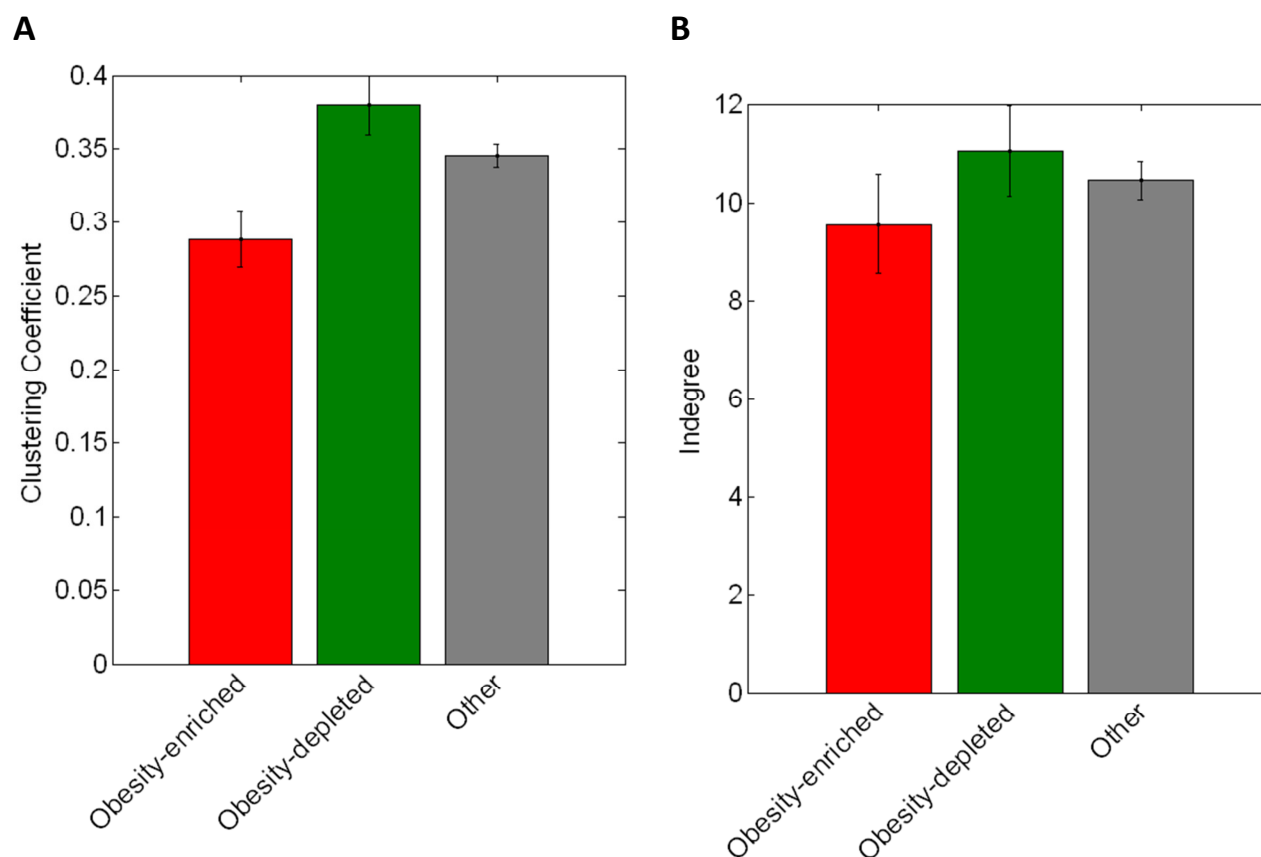
**Fig. S3.** Histogram of differential abundance across the 1563 enzymes found in the global metabolic network. Differential abundance is defined as the  $\log_2$  of the odds ratio of pooled enzyme abundance in obese vs. lean samples. Enzymes with a fold change greater than 1 were classified as 'enriched.' Enzymes with a fold change less than -1 were classified as 'depleted.'



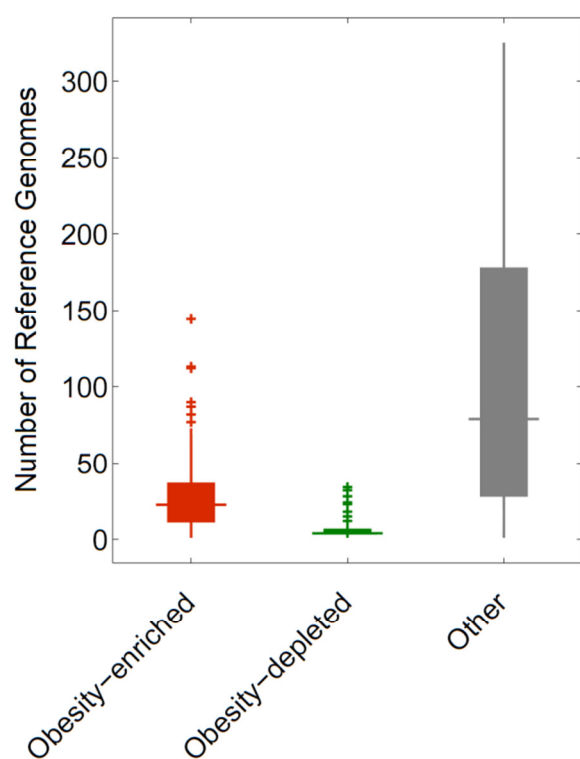
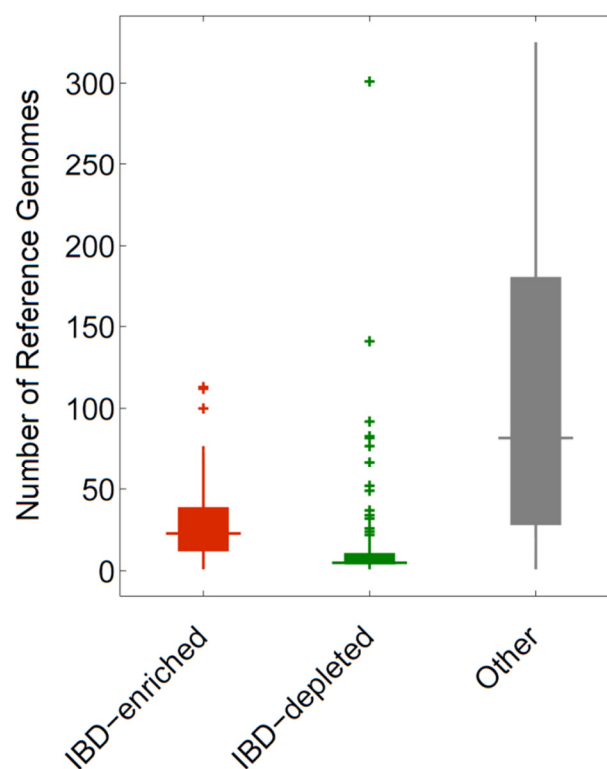
**Fig. S4.** The effect of missing or erroneous annotation data on centrality values in the metabolic network. To determine the effect of incomplete annotation data, we deleted a randomly selected subset of 5%, 10%, 20%, or 30% of the annotations in KEGG, and re-constructed global metabolic networks from the remaining annotated enzymes. Similarly, to simulate the effect of erroneous annotations, we rewired a random subset of 10% of the edges in the network. The mean centrality score and standard deviation (over 100 iterations) of each KO in these perturbed networks is plotted against its centrality score in the fully-annotated network, demonstrating a relatively small sensitivity of centrality scores to annotation inaccuracies. In each case, KO centrality scores in the perturb network are strongly correlated with the original centrality scores. Spearman correlation coefficient: 0.998 (5% deleted), 0.996 (10% deleted), 0.984 (20% deleted), 0.969 (30% deleted), 0.788 (10% rewired).



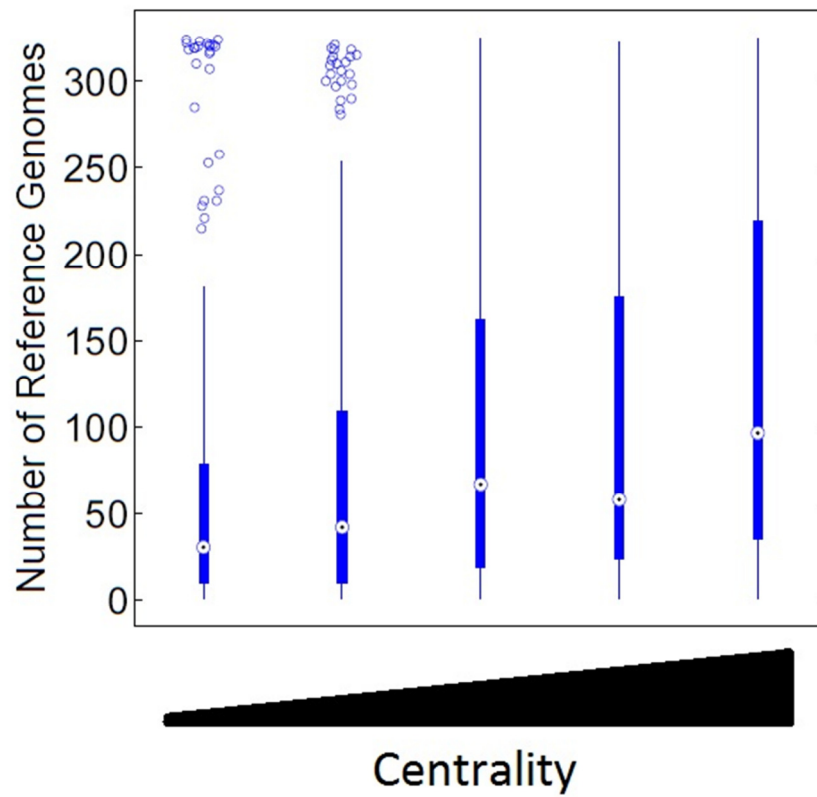
**Fig. S5.** The effect of incomplete enzyme annotation on the relationship between centrality and obesity-associated enzymes. **(A)** Boxplots depicting the distribution of the mean centrality score of enzymes in 100 iterations of networks constructed after randomly deleting 10% of the annotations in KEGG. Mean centrality is calculated across enzymes grouped according to their association with obesity. The mean centrality of these enzyme groups in the fully-annotated network is plotted as a circled X's. Evidently, in these perturbed networks, the centrality of obesity-associated enzymes (as well as obesity-enriched and obesity-depleted enzymes separately) is still significantly lower than the centrality of other enzymes. **(B)** Frequency of obesity-associated vs. other enzymes in different centrality tiers (peripheral, intermediate, and central) in perturbed networks constructed after randomly deleting 10% of the annotations in KEGG. Plotted above are the mean (filled circles) and standard deviation (dotted lines) over 100 such perturbed networks. Circled X's represent the frequency in the fully-annotated network.



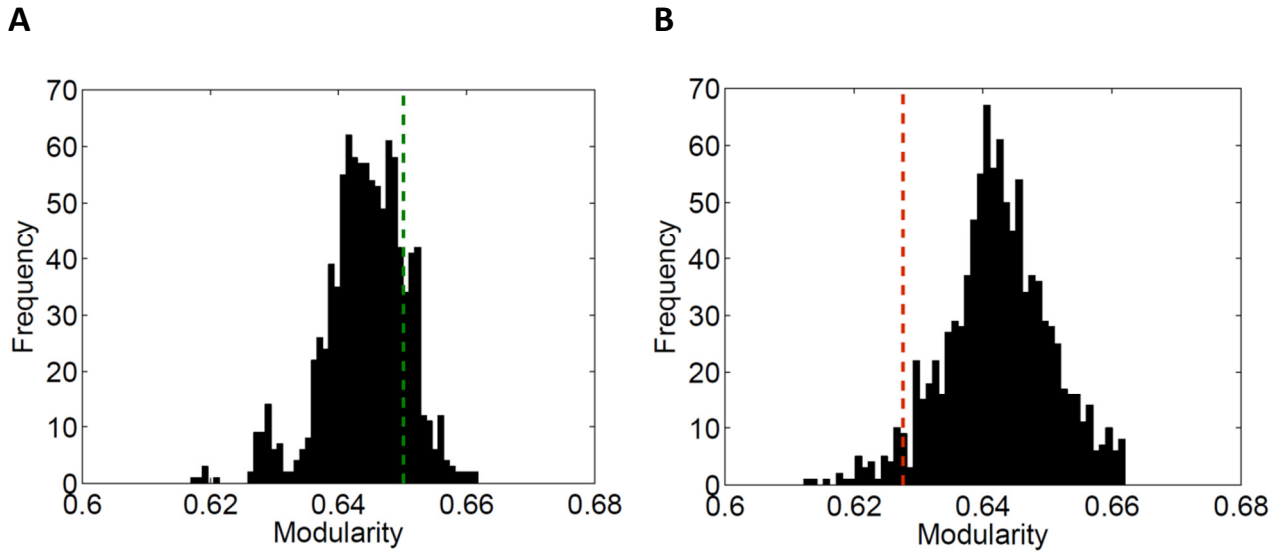
**Fig. S6.** Mean and standard error of the **(A)** clustering coefficient and **(B)** indegree of enriched, depleted, and other enzymes in IBD microbiomes. As with obesity-associated enzymes, IBD-enriched enzymes tend to have a lower clustering coefficient ( $p < 0.015$ ) and lower indegree compared to other enzymes, while IBD-depleted enzymes tend to have a higher clustering coefficient and higher indegree. These differences mostly fall short of statistical significance, possibly due to smaller sample size.

**A****B**

**Fig. S7.** Boxplots of the number of reference genomes (n=326) associated with enzymes of different classes in (A) obese and (B) IBD microbiomes. Enzymes associated with either obesity or IBD are present in far fewer reference genomes ( $p < 2.0 \times 10^{-55}$  [obese];  $p < 2.410^{-57}$  [IBD]; Wilcoxon rank-sum test).

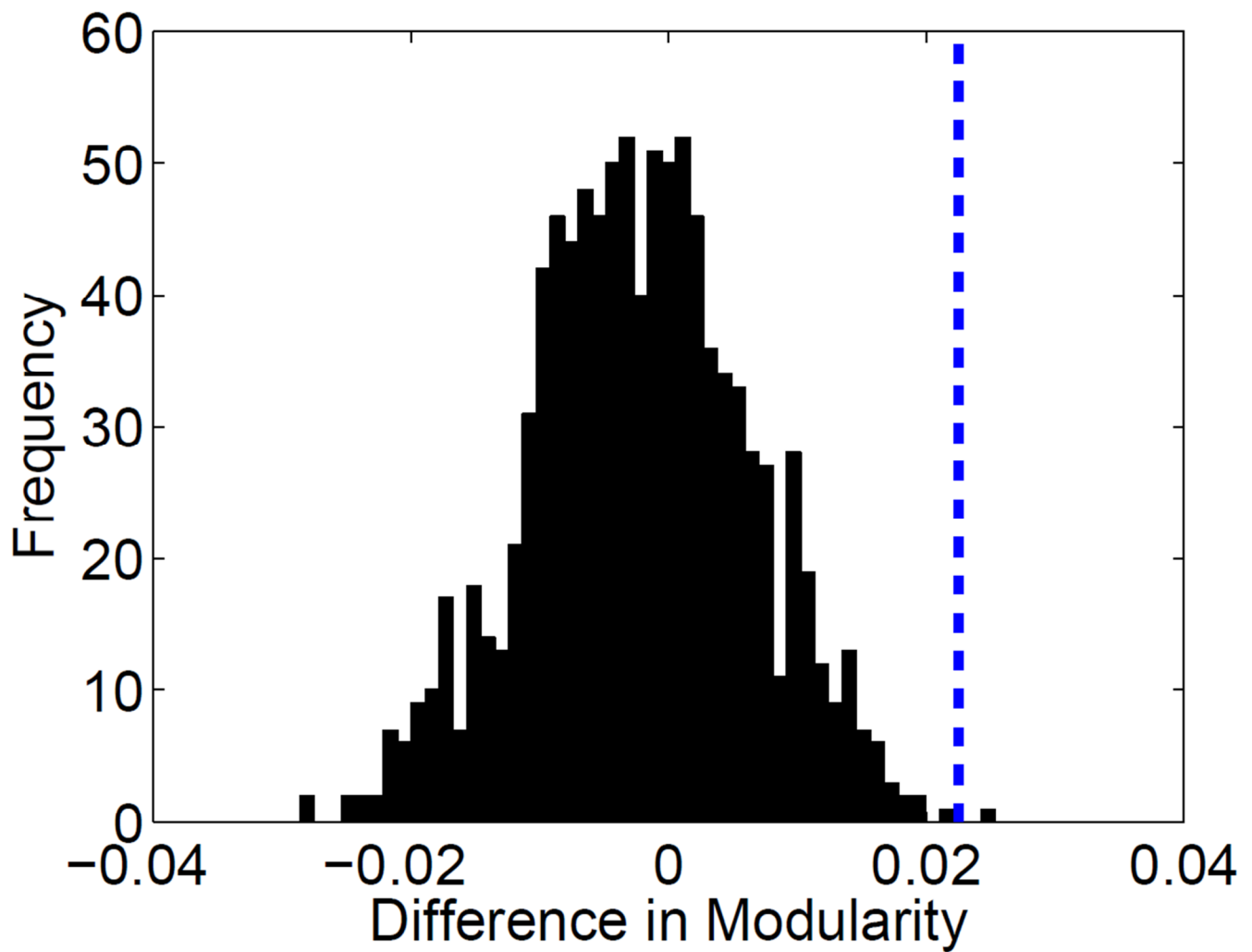


**Fig. S8.** Boxplots of the number of reference genomes (n=326) associated with enzymes in different centrality tiers. Boxes are arranged in order of increasing centrality from left to right. Centrality is positively correlated with the number of associated reference genomes ( $R = 0.23$ ,  $p < 6.0 \times 10^{-18}$ ; Spearman correlation test).

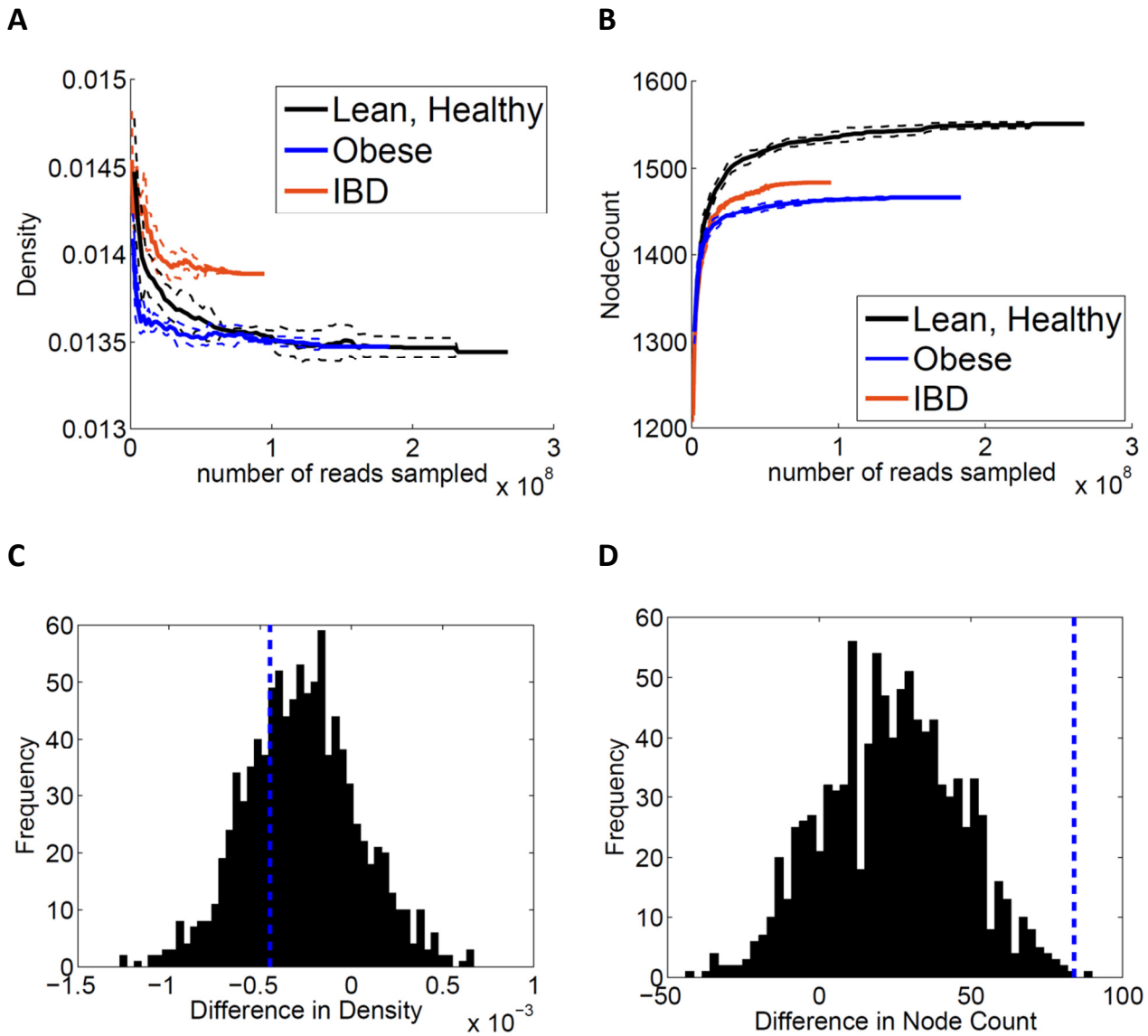


**Fig. S9.** Modularity of **(A)** lean/healthy-specific and **(B)** obese-specific metabolic networks compared to null distributions. To create null distributions, sample labels were randomly shuffled 1,000 times. For each shuffled set, separate lean/healthy and obese-specific networks were constructed and the modularity of each network was calculated (see Supporting Text for more information). Plotted above are histograms of the modularity of these shuffled networks. The modularity of the true lean/healthy-specific network (green dotted line) is higher than the modularity of shuffled networks in most cases (83%) but is not significantly different. In contrast, modularity of the true obese-specific network (red dotted line) is significantly lower than expected ( $p < 0.05$ ).





**Fig. S10.** The difference between the modularity of the obese-specific and lean-healthy-specific network is plotted (dashed blue line) against a null distribution of differences from shuffled networks. To create this null distribution, we created 1,000 pairs of shuffled obese-specific and shuffled lean-healthy-specific networks by randomly rewiring edges in the microbiome-wide network while preserving the indegree and outdegree of each node (see SI Text), and extracting sub-networks corresponding to the enzymes found in samples from a specific host state. The difference in modularity between each corresponding pair of shuffled obese-specific and shuffled lean-healthy-specific network was calculated. In both obese-specific and lean-healthy-specific networks, shuffled networks are significantly less modular than the real network. Yet, the observed difference in modularity in the true networks is significantly greater than the expected difference in the shuffled networks ( $p < 2.0 \times 10^{-3}$ ).



**Fig. S11.** Rarefaction analysis of network density (A) and node count (B) for host-state-specific networks. The (C) difference in density between the lean/healthy-specific and IBD-specific networks and (D) difference in node count between the lean/healthy-specific and obese-specific networks is shown (dotted line) compared to null distributions. Null distributions were generated by shuffling sample labels 1,000 times (see SI Text and Fig. S9 legend). The observed difference between the node count of the lean/healthy and obese-specific networks is statistically greater than expected compared to this null distribution ( $p=0.001$ ).

## Supporting Tables

**Table S1. Sample classes and counts for metagenomic datasets used in this study**

Dataset	Host State	Sample Count	Danish	Spanish
Qin et al. 2010	lean-healthy	60	48	12
	lean-IBD	22	0	22
	obese-healthy	39	37	2
	obese-IBD	3	0	3
Turnbaugh et al. 2009	lean	9		
	obese	9		

Table S2A. Obesity-enriched enzymes

ID	Name	Functional Class	OR - Obesity	Centrality Score	Clustering Coefficient	In-degree
K03862	vanillate monooxygenase [EC:1.14.13.82]	Xenobiotics Biodegradation and Metabolism	33.828	0.00E+00	0.167	0
K00258	NONE	Biosynthesis of Polyketides and Terpenoids/ Xenobiotics Biodegradation and Metabolism	26.684	0.00E+00	0.000	1
K08347	nitrate reductase 2, gamma subunit [EC:1.7.99.4]	Energy Metabolism	13.421	0.00E+00	0.000	0
K02813	PTS system, sorbose-specific IIB component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	12.838	0.00E+00	0.000	0
K01757	strictosidine synthase [EC:4.3.3.2]	Biosynthesis of Other Secondary Metabolites	10.926	0.00E+00	0.000	1
K02301	protoheme IX farnesyltransferase [EC:2.5.1.-]	Energy Metabolism/ Metabolism of Cofactors and Vitamins	8.916	0.00E+00	0.000	1
K02753	PTS system, arbutin-, cellobiose-, and salicin-specific IIC	Membrane Transport/ Carbohydrate Metabolism	8.824	0.00E+00	0.000	0
K00108	choline dehydrogenase [EC:1.1.99.1]	Amino Acid Metabolism	8.474	5.40E-07	0.000	2
K02749	PTS system, arbutin-like IIB component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	8.100	0.00E+00	0.000	0
K10984	PTS system, galactosamine-specific IIB component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	8.079	0.00E+00	0.000	0
K02812	PTS system, sorbose-specific IIA component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	7.868	0.00E+00	0.000	0
K08345	nitrate reductase 2, alpha subunit [EC:1.7.99.4]	Energy Metabolism	7.856	0.00E+00	0.000	0
K08346	nitrate reductase 2, beta subunit [EC:1.7.99.4]	Energy Metabolism	7.678	0.00E+00	0.000	0
K00816	kynurenine-oxoglutarate transaminase [EC:2.6.1.7]	Amino Acid Metabolism	7.409	0.00E+00	0.000	1
K01061	carboxymethylenebutenolidase [EC:3.1.1.45]	Xenobiotics Biodegradation and Metabolism	7.152	0.00E+00	0.000	2
K01117	sphingomyelin phosphodiesterase [EC:3.1.4.12]	Lipid Metabolism	6.383	0.00E+00	0.000	0
K05709	small terminal subunit of phenylpropionate dioxygenase	Amino Acid Metabolism	5.689	0.00E+00	0.000	0
K05712	3-(3-hydroxy-phenyl)propionate hydroxylase [EC:1.14.13.-]	Amino Acid Metabolism	5.163	0.00E+00	0.000	0
K05708	large terminal subunit of phenylpropionate dioxygenase	Amino Acid Metabolism	4.412	0.00E+00	0.000	0
K10986	PTS system, galactosamine-specific IID component	Membrane Transport/ Carbohydrate Metabolism	4.109	0.00E+00	0.000	0
K08092	3-dehydro-L-gulonate 2-dehydrogenase [EC:1.1.1.130]	Carbohydrate Metabolism	3.853	0.00E+00	0.000	0
K00370	nitrate reductase 1, alpha subunit [EC:1.7.99.4]	Signal Transduction/ Energy Metabolism	3.101	0.00E+00	0.000	0
K05286	phosphatidylinositol glycan, class B [EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	2.824	1.62E-06	0.000	1
K08361	nitrate reductase 2, delta subunit [EC:1.7.99.4]	Energy Metabolism	2.764	0.00E+00	0.000	0
K00595	precorrin-6Y C5,15-methyltransferase / precorrin-8W decarboxylase	Metabolism of Cofactors and Vitamins	2.471	0.00E+00	0.000	0
K00801	farnesyl-diphosphate farnesyltransferase [EC:2.5.1.21]	Lipid Metabolism	2.428	0.00E+00	0.000	1
K01083	3-phytase [EC:3.1.3.8]	Carbohydrate Metabolism	2.371	0.00E+00	0.000	1
K02790	PTS system, maltose and glucose-specific IIB component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	2.355	6.40E-07	0.167	2
K11191	PTS system, N-acetylmuramic acid-specific IIB component	Membrane Transport/ Carbohydrate Metabolism	2.351	0.00E+00	0.000	0
K02791	PTS system, maltose and glucose-specific IIC component	Membrane Transport/ Carbohydrate Metabolism	2.268	6.40E-07	0.167	2
K02752	PTS system, arbutin-, cellobiose-, and salicin-specific IIB	Membrane Transport/ Carbohydrate Metabolism	2.214	0.00E+00	0.000	0
K00374	nitrate reductase 1, gamma subunit [EC:1.7.99.4]	Signal Transduction/ Energy Metabolism	2.119	0.00E+00	0.000	0
K04102	4,5-dihydroxyphthalate decarboxylase [EC:4.1.1.55]	Xenobiotics Biodegradation and Metabolism	2.037	0.00E+00	0.167	0
K00450	gentisate 1,2-dioxygenase [EC:1.13.11.4]	Amino Acid Metabolism	inf	0.00E+00	0.000	1
K05368	aquacobalamin reductase / NAD(P)H-flavin reductase [EC:1.16.1.3]	Metabolism of Cofactors and Vitamins	inf	0.00E+00	0.000	3
K00363	nitrite reductase (NAD(P)H) small subunit [EC:1.7.1.4]	Energy Metabolism	13.911	0.00E+00	0.000	12
K06132	putative cardiolipin synthase [EC:2.7.8.-]	Lipid Metabolism	2.302	0.00E+00	0.000	3
K01082	3(2), 5-bisphosphate nucleotidase [EC:3.1.3.7]	Energy Metabolism	inf	1.10E-05	0.500	1
K00508	linoleoyl-CoA desaturase [EC:1.14.19.3]	Lipid Metabolism	30.188	0.00E+00	0.500	2
K08678	UDP-glucuronate decarboxylase [EC:4.1.1.35]	Carbohydrate Metabolism	22.778	0.00E+00	1.000	2
K04071	6-pyruvoyltetrahydropterin 2-reductase [EC:1.1.1.220]	Metabolism of Cofactors and Vitamins	3.591	0.00E+00	0.500	1
K05774	ribose 1,5-bisphosphokinase [EC:2.7.4.23]	Carbohydrate Metabolism	3.202	0.00E+00	0.833	0
K08969	aminotransferase [EC:2.6.1.-]	Amino Acid Metabolism	2.657	0.00E+00	0.250	0
K10782	fatty acyl-ACP thioesterase A [EC:3.1.2.14 3.1.2.-]	Lipid Metabolism	2.217	0.00E+00	1.000	2
K01608	tartronate-semialdehyde synthase [EC:4.1.1.47]	Carbohydrate Metabolism	11.600	3.84E-05	0.438	16
K04568	lysyl-tRNA synthetase, class II [EC:6.1.1.6]	Translation	6.552	0.00E+00	0.600	5
K00932	propionate kinase [EC:2.7.2.15]	Carbohydrate Metabolism	4.697	0.00E+00	1.000	6
K04022	alcohol dehydrogenase	Carbohydrate Metabolism	3.895	0.00E+00	0.763	16
K05352	ribitol-5-phosphate 2-dehydrogenase [EC:1.1.1.137]	Carbohydrate Metabolism	3.422	0.00E+00	0.694	7
K10046	GDP-D-mannose 3, 5-epimerase [EC:5.1.3.18 5.1.3.-]	Carbohydrate Metabolism	2.986	0.00E+00	0.500	3
K02344	DNA polymerase III subunit psi [EC:2.7.7.7]	Replication and Repair/ Nucleotide Metabolism	2.628	1.21E-05	0.774	19
K01674	carbonic anhydrase [EC:4.2.1.1]	Energy Metabolism	2.548	0.00E+00	0.377	25
K00070	3beta-hydroxy-delta5-steroid dehydrogenase / steroid delta-isomerase	Lipid Metabolism	2.514	1.47E-05	0.300	3
K01475	NONE	Amino Acid Metabolism/ Nucleotide Metabolism/ Xenobiotics Biodegradation and Metabolism	2.169	0.00E+00	0.889	10
K00461	arachidonate 5-lipoxygenase [EC:1.13.11.34]	Lipid Metabolism	inf	1.48E-03	0.167	2
K05783	1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate dehydrogenase	Xenobiotics Biodegradation and Metabolism	inf	2.44E-03	0.000	2
K00103	L-gulonolactone oxidase [EC:1.1.3.8]	Carbohydrate Metabolism	11.892	5.21E-03	0.000	1
K07251	thiamine kinase [EC:2.7.1.89]	Metabolism of Cofactors and Vitamins	10.481	5.45E-05	0.000	1
K01484	succinylarginine dihydrolase [EC:3.5.3.23]	Amino Acid Metabolism	8.859	4.23E-03	0.000	1
K03184	2-octaprenyl-3-methyl-6-methoxy-1,4-benzoquinol hydroxylase	Metabolism of Cofactors and Vitamins	7.649	9.02E-03	0.000	2
K01521	CDP-diacylglycerol pyrophosphatase [EC:3.6.1.26]	Lipid Metabolism	7.397	9.61E-04	0.000	1
K00151	5-carboxymethyl-2-hydroxymuconic-semialdehyde dehydrogenase	Amino Acid Metabolism	6.154	4.49E-03	0.000	1
K05713	2,3-dihydroxyphenylpropionate 1,2-dioxygenase [EC:1.13.11.16]	Amino Acid Metabolism	5.715	7.78E-03	0.000	2
K06447	succinylglutamic semialdehyde dehydrogenase [EC:1.2.1.71]	Amino Acid Metabolism	5.534	4.36E-03	0.000	1
K03185	2-octaprenyl-6-methoxyphenol hydroxylase [EC:1.14.13.-]	Metabolism of Cofactors and Vitamins	5.237	3.09E-03	0.000	1
K05939	acyl-[acyl-carrier-protein]-phospholipid O-acyltransferase /	Lipid Metabolism	5.213	1.15E-03	0.054	1
K03119	taurine dioxygenase [EC:1.14.11.17]	Metabolism of Other Amino Acids	4.537	4.67E-03	0.167	2
K04561	nitric-oxide reductase, cytochrome b-containing subunit I	Energy Metabolism	3.288	3.88E-04	0.000	1
K00840	succinylornithine aminotransferase [EC:2.6.1.81]	Amino Acid Metabolism	3.114	4.30E-03	0.000	1
K09471	gamma-glutamylputrescine oxidase [EC:1.4.3.-]	Amino Acid Metabolism	2.904	3.19E-03	0.000	1
K09472	gamma-glutamyl-gamma-aminobutyraldehyde dehydrogenase [EC:1.2.1.1-]	Amino Acid Metabolism	2.471	3.26E-03	0.000	1
K01772	ferrochelatase [EC:4.99.1.1]	Metabolism of Cofactors and Vitamins	2.156	1.05E-03	0.000	2
K02549	O-succinylbenzoate synthase [EC:4.2.1.113]	Metabolism of Cofactors and Vitamins	2.025	2.09E-03	0.000	1
K00465	NONE	Xenobiotics Biodegradation and Metabolism	inf	1.91E-03	0.107	6
K00613	glycine amidinotransferase [EC:2.1.4.1]	Amino Acid Metabolism	inf	1.92E-02	0.138	27
K01047	phospholipase A2 [EC:3.1.1.4]	Signal Transduction/ Lipid Metabolism/Circulatory System	11.405	6.67E-03	0.115	5
K02079	N-acetylgalactosamine-6-phosphate deacetylase [EC:3.5.1.25]	Carbohydrate Metabolism	8.194	3.33E-03	0.050	4
K03788	acid phosphatase (class B) [EC:3.1.3.2]	Metabolism of Cofactors and Vitamins/ Xenobiotics Biodegradation and Metabolism	7.738	2.28E-03	0.000	3
K01825	3-hydroxyacyl-CoA dehydrogenase / enoyl-CoA hydratase /	Amino Acid Metabolism/ Biosynthesis of Polyketides and Terpenoids/ Carbohydrate Metabolism	7.621	1.30E-02	0.203	32
K02554	2-keto-4-pentenote hydratase [EC:4.2.1.80]	Amino Acid Metabolism/ Xenobiotics Biodegradation and Metabolism	7.469	4.55E-03	0.000	3
K01782	3-hydroxyacyl-CoA dehydrogenase / enoyl-CoA hydratase /	Amino Acid Metabolism/ Biosynthesis of Polyketides and Terpenoids/ Carbohydrate Metabolism	5.661	1.30E-02	0.203	32
K09251	putrescine aminotransferase [EC:2.6.1.82]	Amino Acid Metabolism	4.835	1.26E-03	0.189	3
K05711	2,3-dihydroxy-2,3-dihydrophenylpropionate dehydrogenase [EC:1.3.1.1-]	Amino Acid Metabolism	4.720	5.56E-03	0.000	4
K00383	glutathione reductase (NADPH) [EC:1.8.1.7]	Metabolism of Other Amino Acids	4.685	1.62E-02	0.203	5
K00481	p-hydroxybenzoate 3-monoxygenase [EC:1.14.13.2]	Xenobiotics Biodegradation and Metabolism	3.904	8.65E-03	0.146	8
K08723	5-nucleotidase [EC:3.1.3.5]	Metabolism of Cofactors and Vitamins/ Nucleotide Metabolism	3.145	1.62E-02	0.192	52
K00276	primary-amine oxidase [EC:1.4.3.21]	Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites/ Metabolism of Other Amino Acids	2.406	3.46E-02	0.121	11
K01093	4-phytase / acid phosphatase [EC:3.1.3.26 3.1.3.2]	Carbohydrate Metabolism/ Metabolism of Cofactors and Vitamins/ Xenobiotics Biodegradation and ...	2.255	3.39E-03	0.000	4
K04110	benzoate-CoA ligase [EC:6.2.1.25]	Xenobiotics Biodegradation and Metabolism	2.169	1.17E-03	0.000	3
K01031	3-oxoadipate CoA-transferase, alpha subunit [EC:2.8.3.6]	Xenobiotics Biodegradation and Metabolism	inf	8.84E-03	0.333	1
K09473	gamma-glutamyl-gamma-aminobutyrate hydrolase [EC:3.5.1.94]	Amino Acid Metabolism/ Enzyme Families	12.292	3.32E-03	0.300	1
K05526	succinylglutamate desuccinylase [EC:3.5.1.96]	Amino Acid Metabolism	8.691	4.43E-03	0.401	1
K02293	phytoene dehydrogenase, phytoene desaturase [EC:1.14.99.-]	Biosynthesis of Polyketides and Terpenoids	5.559	5.22E-04	0.500	2
K07751	Pepp aminopeptidase [EC:3.4.11.23]	Enzyme Families/ Metabolism of Other Amino Acids	5.453	9.70E-04	0.217	1
K00137	aminobutyraldehyde dehydrogenase [EC:1.2.1.19]	Amino Acid Metabolism/ Metabolism of Other Amino Acids	4.686	7.33E-04	0.367	2
K01561	haloacetate dehalogenase [EC:3.8.1.3]	Xenobiotics Biodegradation and Metabolism	3.627	1.93E-04	0.639	1
K02496	uroporphyrin-III C-methyltransferase [EC:2.1.1.107]	Metabolism of Cofactors and Vitamins	3.580	5.25E-04	0.333	1
K05915	NONE	Xenobiotics Biodegradation and Metabolism	3.535	5.31E-03	0.214	2
K03081	3-dehydro-L-gulonate-6-phosphate decarboxylase [EC:4.1.1.85]	Carbohydrate Metabolism	2.852	2.77E-03	0.500	2
K09699	2-oxoisovalerate dehydrogenase E2 component (dihydrolipoyl	Amino Acid Metabolism	2.405	3.88E-04	0.250	2
K01597	diphosphomevalonate decarboxylase [EC:4.1.1.33]	Biosynthesis of Polyketides and Terpenoids	2.222	1.65E-02	0.250	1

K08687	N-carbamoylsarcosine amidase [EC:3.5.1.59]	Amino Acid Metabolism	2.105	2.22E-03	0.238	2
K04782	isochorismate pyruvate-lyase [EC:4.1.3.-]	Biosynthesis of Polyketides and Terpenoids	Inf	2.24E-04	0.400	3
K00467	lactate 2-monooxygenase [EC:1.13.12.4]	Carbohydrate Metabolism	Inf	1.32E-04	0.607	3
K00255	long-chain-acyl-CoA dehydrogenase [EC:1.3.99.13]	Lipid Metabolism/Endocrine System	Inf	2.98E-04	0.464	5
K10353	deoxyadenosine kinase [EC:2.7.1.76]	Nucleotide Metabolism	Inf	7.78E-05	0.893	7
K01510	aprase [EC:3.6.1.5]	Signaling Molecules and Interaction/ Nucleotide Metabolism	24.418	1.26E-02	0.266	63
K01252	enterobactin isochorismatase [EC:3.3.2.1]	Biosynthesis of Polyketides and Terpenoids	23.498	5.22E-04	0.500	3
K02509	2-oxo-hept-3-ene-1,7-dioate hydratase [EC:4.2.1.-]	Amino Acid Metabolism	21.389	5.47E-03	0.333	3
K00247	fumarate reductase subunit D [EC:1.3.99.1]	Signal Transduction/ Carbohydrate Metabolism/ Energy Metabolism	17.946	3.88E-04	0.612	28
K00158	pyruvate oxidase [EC:1.2.3.3]	Carbohydrate Metabolism	17.624	4.39E-03	0.535	35
K11472	glycolate oxidase FAD binding subunit	Carbohydrate Metabolism	14.707	1.35E-04	0.515	7
K00291	saccharopine dehydrogenase (NADP+, L-lysine forming) [EC:1.5.1.8]	Amino Acid Metabolism	12.949	7.71E-05	0.309	5
K00892	inosine kinase [EC:2.7.1.73]	Nucleotide Metabolism	12.533	4.26E-03	0.422	23
K00246	fumarate reductase subunit C [EC:1.3.99.1]	Signal Transduction/ Carbohydrate Metabolism/ Energy Metabolism	11.668	3.88E-04	0.612	28
K01637	isocitrate lyase [EC:4.1.3.1]	Carbohydrate Metabolism	11.103	2.65E-03	0.410	4
K02560	lipid A biosynthesis (KDO)2-(lauroyl)-lipid iva acyltransferase	Glycan Biosynthesis and Metabolism	10.979	3.24E-04	0.446	5
K11177	xanthine dehydrogenase YagR molybdenum-binding subunit [EC:1.17.1.4]	Nucleotide Metabolism	9.356	6.95E-04	0.615	11
K00455	3,4-dihydroxyphenylacetate 2,3-dioxygenase [EC:1.13.11.15]	Amino Acid Metabolism	8.975	6.63E-03	0.333	4
K09470	gamma-glutamylputrescine synthase [EC:6.3.1.11]	Amino Acid Metabolism	8.773	3.12E-03	0.299	23
K03782	catalase/peroxidase [EC:1.11.1.6]	Amino Acid Metabolism/ Energy Metabolism	8.651	1.18E-04	0.267	3
K01682	aconitate hydratase 2 [EC:4.2.1.3]	Carbohydrate Metabolism/ Energy Metabolism	8.546	5.50E-04	0.357	4
K00631	glycerol-3-phosphate O-acyltransferase [EC:2.3.1.15]	Lipid Metabolism	8.456	7.09E-03	0.536	7
K05851	adenylate cyclase, class 1 [EC:4.6.1.1]	Infectious Diseases/ Nucleotide Metabolism	8.112	2.08E-04	0.939	32
K03181	chorismate-pyruvate lyase [EC:4.1.3.40]	Metabolism of Cofactors and Vitamins	7.700	4.87E-03	0.303	15
K05921	5-oxopent-3-ene-1,2,5-tricarboxylate decarboxylase /	Amino Acid Metabolism	7.670	2.11E-03	0.333	3
K00242	succinate dehydrogenase hydrophobic membrane anchor protein	Carbohydrate Metabolism/ Energy Metabolism/ Xenobiotics Biodegradation and Metabolism	7.647	3.88E-04	0.612	28
K06116	glycerol 3-phosphatase 1 [EC:3.1.3.21]	Lipid Metabolism	7.257	1.37E-03	0.363	7
K01638	malate synthase [EC:2.3.3.9]	Carbohydrate Metabolism	6.655	1.79E-02	0.310	55
K01690	phosphogluconate dehydrogenase [EC:4.2.1.12]	Carbohydrate Metabolism	6.602	2.39E-03	0.333	3
K00673	arginine N-succinyltransferase [EC:2.3.1.109]	Amino Acid Metabolism	6.380	4.16E-03	0.333	3
K01087	trehalose-phosphatase [EC:3.1.3.12]	Carbohydrate Metabolism	6.240	4.13E-03	0.250	7
K03472	D-erythrose 4-phosphate dehydrogenase [EC:1.2.1.72]	Metabolism of Cofactors and Vitamins	5.991	1.95E-03	0.452	4
K00049	glyoxylate reductase (NADP+) [EC:1.1.1.79]	Carbohydrate Metabolism	5.912	1.19E-02	0.217	29
K00146	phenylacetaldehyde dehydrogenase [EC:1.2.1.39]	Amino Acid Metabolism/ Xenobiotics Biodegradation and Metabolism	5.815	1.58E-04	0.405	6
K08348	formate dehydrogenase-N, alpha subunit [EC:1.2.1.2]	Signal Transduction/ Carbohydrate Metabolism/ Energy Metabolism	5.645	4.05E-03	0.247	38
K00116	malate dehydrogenase (quinone) [EC:1.1.5.4]	Carbohydrate Metabolism	5.594	1.73E-03	0.477	27
K01593	aromatic-L-amino-acid decarboxylase [EC:4.1.1.28]	Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites	5.217	8.31E-03	0.217	20
K00815	tyrosine aminotransferase [EC:2.6.1.5]	Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites/ Metabolism of Cofactors and Vitamins	5.199	3.28E-03	0.361	15
K02802	PTS system, N-acetylglucosamine-specific IIA component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	5.193	1.98E-03	0.333	4
K01595	phosphoenolpyruvate carboxylase [EC:4.1.1.31]	Carbohydrate Metabolism/ Energy Metabolism	5.127	5.57E-03	0.292	31
K03777	D-lactate dehydrogenase [EC:1.1.1.28]	Carbohydrate Metabolism	4.984	8.83E-04	0.509	35
K01584	arginine decarboxylase [EC:4.1.1.19]	Amino Acid Metabolism	4.783	4.09E-04	0.333	3
K01460	glutathionylspermidine amidase/synthetase [EC:3.5.1.78 6.3.1.8]	Metabolism of Other Amino Acids	4.514	4.13E-03	0.347	6
K03815	xanthosine phosphorylase [EC:2.4.2.-]	Nucleotide Metabolism	4.449	3.58E-04	0.615	13
K00163	pyruvate dehydrogenase E1 component [EC:1.2.4.1]	Amino Acid Metabolism/ Carbohydrate Metabolism	4.405	2.66E-03	0.452	46
K00117	quinoprotein glucose dehydrogenase [EC:1.1.5.2]	Carbohydrate Metabolism	4.239	9.26E-03	0.319	12
K08349	formate dehydrogenase-N, beta subunit [EC:1.2.1.2]	Signal Transduction/ Carbohydrate Metabolism/ Energy Metabolism	4.190	4.05E-03	0.247	38
K06445	acyl-CoA dehydrogenase [EC:1.3.99.-]	Lipid Metabolism	4.125	7.97E-04	0.478	13
K00121	S-(hydroxymethyl)glutathione dehydrogenase / alcohol dehydrogenase	Amino Acid Metabolism/ Carbohydrate Metabolism/ Energy Metabolism/ Lipid Metabolism	4.002	1.15E-02	0.320	25
K01908	propionyl-CoA synthetase [EC:6.2.1.17]	Carbohydrate Metabolism/ Lipid Metabolism	3.995	2.05E-04	0.560	18
K01524	guanosine-5-triphosphate,3-diphosphate pyrophosphatase	Nucleotide Metabolism	3.945	1.11E-03	0.333	4
K00028	malate dehydrogenase (decarboxylating) [EC:1.1.1.39]	Carbohydrate Metabolism/ Energy Metabolism	3.615	1.93E-02	0.227	43
K01483	ureidoglycolate hydrolase [EC:3.5.3.19]	Nucleotide Metabolism	3.520	2.16E-02	0.222	49
K04781	salicylate synthetase [EC:5.4.2.4.1.3.-]	Biosynthesis of Polyketides and Terpenoids	3.436	5.87E-03	0.345	10
K06118	UDP-sulfoquinovose synthase [EC:3.13.1.1]	Carbohydrate Metabolism/ Lipid Metabolism	3.134	6.27E-04	0.600	4
K01011	3-mercaptopyruvate sulfurtransferase [EC:2.8.1.2]	Amino Acid Metabolism	3.102	8.26E-03	0.425	9
K01085	glucose-1-phosphatase [EC:3.1.3.10]	Carbohydrate Metabolism	3.098	5.74E-03	0.471	9
K00101	L-lactate dehydrogenase (cytochrome) [EC:1.1.2.3]	Carbohydrate Metabolism	3.017	1.57E-04	0.596	3
K06210	nicotinamide mononucleotide adenyllyltransferase [EC:2.7.7.1]	Metabolism of Cofactors and Vitamins	2.625	8.76E-03	0.456	18
K00436	hydrogen dehydrogenase [EC:1.12.1.2]	Carbohydrate Metabolism/ Energy Metabolism	2.507	4.43E-03	0.508	12
K03462	nicotinamide phosphoribosyltransferase [EC:2.4.2.12]	Metabolism of Cofactors and Vitamins	2.475	1.24E-03	0.538	8
K00045	mannitol 2-dehydrogenase [EC:1.1.1.67]	Carbohydrate Metabolism	2.471	9.24E-04	0.346	9
K00693	glycogen(starch) synthase [EC:2.4.1.11]	Carbohydrate Metabolism/ Glycan Biosynthesis and Metabolism/Endocrine System	2.460	1.56E-04	0.467	4
K05823	N-acetyldiaminopimelate deacetylase [EC:3.5.1.47]	Amino Acid Metabolism	2.443	2.22E-03	0.333	4
K00365	urate oxidase [EC:1.7.3.3]	Biosynthesis of Other Secondary Metabolites/ Nucleotide Metabolism	2.435	1.04E-03	0.500	3
K02552	menaquinone-specific isochorismate synthase [EC:5.4.4.2]	Biosynthesis of Polyketides and Terpenoids/ Metabolism of Cofactors and Vitamins	2.382	3.12E-03	0.422	10
K00364	GMP reductase [EC:1.7.1.7]	Nucleotide Metabolism	2.261	1.92E-04	0.505	12
K08350	formate dehydrogenase-N, gamma subunit [EC:1.2.1.2]	Signal Transduction/ Carbohydrate Metabolism/ Energy Metabolism	2.234	4.05E-03	0.247	38
K00886	polyphosphate glucokinase [EC:2.7.1.63]	Carbohydrate Metabolism	2.162	2.23E-03	0.303	23

**Table S2B. Obesity-depleted enzymes**

ID	Name	Functional Class	OR - Obesity	Centrality Score	Clustering Coefficient	In-degree
K07635	galactoside alpha-1,3-fucosyltransferase 7 [EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	0.000	0.00E+00	0.000	1
K00888	phosphatidylinositol 4-kinase [EC:2.7.1.67]	Signal Transduction/ Carbohydrate Metabolism	0.000	0.00E+00	0.000	0
K00902	dolichol kinase [EC:2.7.1.108]	Glycan Biosynthesis and Metabolism	0.000	0.00E+00	0.000	0
K01110	phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase [EC:3.1.3.67]	Cell Communication/ Cell Growth and Death/ Signal Tr...	0.000	0.00E+00	0.000	0
K03852	sulfoacetaldehyde acetyltransferase [EC:2.3.3.15]	Metabolism of Other Amino Acids	0.000	0.00E+00	0.189	0
K03863	vanillate monooxygenase [EC:1.14.13.82]	Xenobiotics Biodegradation and Metabolism	0.000	0.00E+00	0.167	0
K04107	4-hydroxybenzoyl-CoA reductase subunit 1 [EC:1.3.99.20]	Xenobiotics Biodegradation and Metabolism	0.000	0.00E+00	0.000	0
K08686	2-chlorobenzoate 1,2-dioxygenase [EC:1.14.12.13]	Xenobiotics Biodegradation and Metabolism	0.000	0.00E+00	0.000	0
K09881	acylglycerol kinase [EC:2.7.1.94]	Lipid Metabolism	0.000	2.70E-05	0.000	1
K10572	inositol-pentakisphosphate 2-kinase [EC:2.7.1.158]	Signal Transduction/ Carbohydrate Metabolism	0.000	0.00E+00	0.000	0
K01099	phosphatidylinositol-bisphosphatase [EC:3.1.3.36]	Signal Transduction/ Carbohydrate Metabolism	0.000	8.10E-07	0.000	2
K01556	kyureninase [EC:3.7.1.3]	Amino Acid Metabolism	0.000	6.80E-06	0.050	1
K03896	acetyl CoA:N6-hydroxylysine acetyl transferase [EC:2.3.1.102]	Amino Acid Metabolism	0.006	0.00E+00	0.000	1
K01001	UDP-N-acetylglucosamine-dolichyl-phosphate	Glycan Biosynthesis and Metabolism	0.116	1.62E-06	0.000	1
K04103	indolepyruvate decarboxylase [EC:4.1.1.74]	Amino Acid Metabolism	0.119	0.00E+00	0.000	0
K03330	glutamyl-tRNA(Gln) amidotransferase subunit E [EC:6.3.5.7]	Translation	0.181	0.00E+00	0.000	1
K01233	chitosanase [EC:3.2.1.132]	Carbohydrate Metabolism	0.207	0.00E+00	0.000	1
K01106	inositol-1,4,5-trisphosphate 5-phosphatase [EC:3.1.3.56]	Signal Transduction/ Carbohydrate Metabolism	0.209	0.00E+00	0.000	2
K04708	3-dehydroshinganine reductase [EC:1.1.1.102]	Lipid Metabolism	0.244	0.00E+00	0.000	0
K05710	ferredoxin subunit of phenylpropionate dioxygenase	Amino Acid Metabolism	0.256	0.00E+00	0.000	0
K05797	4-cresol dehydrogenase (hydroxylating) [EC:1.17.99.1]	Xenobiotics Biodegradation and Metabolism	0.311	0.00E+00	0.000	1
K05356	trans-octaprenyltransferase [EC:2.5.1.11]	Biosynthesis of Polyketides and Terpenoids	0.348	1.62E-06	0.000	1
K04109	4-hydroxybenzoyl-CoA reductase subunit 3 [EC:1.3.99.20]	Xenobiotics Biodegradation and Metabolism	0.357	0.00E+00	0.000	0
K01140	arylalkylphosphatase [EC:3.1.8.1]	Xenobiotics Biodegradation and Metabolism	0.389	0.00E+00	0.000	0
K05363	serine/alanine adenylylating enzyme [EC:2.3.2.10]	Glycan Biosynthesis and Metabolism	0.410	0.00E+00	0.000	1
K05296	3(or 17)beta-hydroxysteroid dehydrogenase [EC:1.1.1.51]	Lipid Metabolism	0.000	1.65E-05	0.200	5
K05288	phosphatidylinositol glycan, class O	Glycan Biosynthesis and Metabolism	0.323	0.00E+00	0.000	4
K00039	ribitol 2-dehydrogenase [EC:1.1.1.56]	Carbohydrate Metabolism	0.000	0.00E+00	1.000	2
K00514	zeta-carotene desaturase [EC:1.14.99.30]	Biosynthesis of Polyketides and Terpenoids	0.000	0.00E+00	1.000	2
K08233	polynucleotide-aldehyde esterase [EC:3.1.1.78]	Biosynthesis of Other Secondary Metabolites	0.000	0.00E+00	0.550	0
K08766	carnitine O-palmitoyltransferase 2 [EC:2.3.1.21]	Lipid Metabolism/Endocrine System	0.041	0.00E+00	0.433	2
K05601	hydroxylamine reductase [EC:1.7.99.1]	Energy Metabolism	0.152	0.00E+00	0.696	0

K10207	testosterone 17beta-dehydrogenase (NADP+)	[EC:1.1.1.64]	Lipid Metabolism	0.209	0.00E+00	0.833	2
K03795	sirohdrochlorin cobaltochelatas	[EC:4.99.1.3]	Metabolism of Cofactors and Vitamins	0.260	2.70E-07	0.500	2
K00071	11beta-hydroxysteroid dehydrogenase	[EC:1.1.1.146]	Lipid Metabolism/Excretory System	0.269	6.89E-06	0.333	2
K01075	4-hydroxybenzoyl-CoA thioesterase	[EC:3.1.2.23]	Metabolism of Cofactors and Vitamins/ Xenobiotics Biodegradation and Metabolism	0.300	0.00E+00	0.400	0
K01131	steryl-sulfatase	[EC:3.1.6.2]	Lipid Metabolism	0.495	0.00E+00	1.000	0
K00808	homospermidine synthase	[EC:2.5.1.44]	Biosynthesis of Other Secondary Metabolites	0.000	0.00E+00	0.500	4
K05826	lysine biosynthesis protein LysW		Amino Acid Metabolism	0.000	0.00E+00	1.000	6
K11160	diacylglycerol O-acyltransferase 2	[EC:2.3.1.20 2.3.1.76]	Lipid Metabolism/ Metabolism of Cofactors and Vitamins	0.000	0.00E+00	0.861	9
K01969	3-methylcrotonyl-CoA carboxylase beta subunit	[EC:6.4.1.4]	Amino Acid Metabolism	0.000	0.00E+00	0.900	6
K05605	3-hydroxyisobutyryl-CoA hydrolase	[EC:3.1.2.4]	Amino Acid Metabolism/ Carbohydrate Metabolism/ Metabolism of Other Amino Acids	0.000	1.15E-05	0.800	4
K11151	retinol dehydrogenase 10	[EC:1.1.1.-]	Metabolism of Cofactors and Vitamins	0.000	0.00E+00	0.700	7
K11420	euchromatic histone-lysine N-methyltransferase	[EC:2.1.1.43]	Replication and Repair/ Amino Acid Metabolism	0.000	0.00E+00	0.800	4
K11422	histone-lysine N-methyltransferase SETD1	[EC:2.1.1.43]	Replication and Repair/ Amino Acid Metabolism	0.000	0.00E+00	0.800	4
K02324	DNA polymerase epsilon subunit 1	[EC:2.7.7.7]	Replication and Repair/ Nucleotide Metabolism	0.000	1.21E-05	0.774	19
K02327	DNA polymerase delta subunit 1	[EC:2.7.7.7]	Replication and Repair/ Nucleotide Metabolism	0.000	1.21E-05	0.774	19
K00442	coenzyme F420 hydrogenase delta subunit		Metabolism of Cofactors and Vitamins	0.097	0.00E+00	1.000	4
K00440	coenzyme F420 hydrogenase alpha subunit	[EC:1.12.98.1]	Metabolism of Cofactors and Vitamins	0.106	0.00E+00	1.000	4
K06863	5-formaminoimidazole-4-carboxamide-1-(beta)-D-ribofuranosyl		Nucleotide Metabolism	0.165	2.83E-06	0.476	4
K02322	DNA polymerase II large subunit	[EC:2.7.7.7]	Replication and Repair/ Nucleotide Metabolism	0.177	1.21E-05	0.774	19
K11150	retinol dehydrogenase 8	[EC:1.1.1.-]	Metabolism of Cofactors and Vitamins	0.180	0.00E+00	0.700	7
K02323	DNA polymerase II small subunit	[EC:2.7.7.7]	Replication and Repair/ Nucleotide Metabolism	0.215	1.21E-05	0.774	19
K00251	3-oxo-5-beta-steroid 4-dehydrogenase	[EC:1.3.1.3]	Lipid Metabolism	0.225	1.51E-05	0.350	4
K00443	coenzyme F420 hydrogenase gamma subunit	[EC:1.12.98.1]	Metabolism of Cofactors and Vitamins	0.251	0.00E+00	1.000	4
K05827	lysine biosynthesis protein LysX		Amino Acid Metabolism	0.263	0.00E+00	1.000	6
K02319	DNA polymerase I	[EC:2.7.7.7]	Replication and Repair/ Nucleotide Metabolism	0.264	1.21E-05	0.774	19
K01574	acetacetate decarboxylase	[EC:4.1.1.4]	Carbohydrate Metabolism/ Lipid Metabolism	0.315	0.00E+00	0.732	7
K11154	retinol dehydrogenase 16	[EC:1.1.1.-]	Metabolism of Cofactors and Vitamins	0.423	0.00E+00	0.700	7
K00709	histo-blood group ABO system transferase	[EC:2.4.1.40 2.4.1.37]	Glycan Biosynthesis and Metabolism	0.430	0.00E+00	1.000	3
K01762	1-aminocyclopropane-1-carboxylate synthase	[EC:4.4.1.14]	Amino Acid Metabolism	0.000	1.94E-03	0.000	1
K06123	1-acylglycerone phosphate reductase	[EC:1.1.1.101]	Lipid Metabolism	0.000	1.11E-03	0.000	1
K00968	choline-phosphate cytidyltransferase	[EC:2.7.7.15]	Lipid Metabolism/ Metabolism of Other Amino Acids	0.000	3.64E-03	0.000	2
K03464	muconolactone D-isomerase	[EC:5.3.3.4]	Xenobiotics Biodegradation and Metabolism	0.000	5.00E-03	0.167	2
K05858	phospholipase C, beta	[EC:3.1.4.11]	Cell Communication/ Signal Transduction/ Neurodegenerative Disease	0.000	4.44E-03	0.067	2
K00319	methylenetetrahydromethanopterin dehydrogenase	[EC:1.5.99.9]	Metabolism of Cofactors and Vitamins	0.133	2.43E-02	0.000	2
K01499	methylenetetrahydromethanopterin cyclohydrolase	[EC:3.5.4.27]	Energy Metabolism/ Metabolism of Cofactors and Vitamins	0.375	2.53E-02	0.000	2
K00448	protocatechuate 3,4-dioxygenase, alpha subunit	[EC:1.13.11.3]	Xenobiotics Biodegradation and Metabolism	0.000	6.86E-04	0.150	4
K00449	protocatechuate 3,4-dioxygenase, beta subunit	[EC:1.13.11.3]	Xenobiotics Biodegradation and Metabolism	0.000	6.86E-04	0.150	4
K04100	protocatechuate 4,5-dioxygenase, alpha chain	[EC:1.13.11.8]	Xenobiotics Biodegradation and Metabolism	0.000	1.47E-03	0.071	4
K04101	protocatechuate 4,5-dioxygenase, beta chain	[EC:1.13.11.8]	Xenobiotics Biodegradation and Metabolism	0.000	1.47E-03	0.071	4
K05549	benzoate 1,2-dioxygenase alpha subunit	[EC:1.14.12.10]	Xenobiotics Biodegradation and Metabolism	0.000	6.30E-04	0.000	3
K00446	catechol 2,3-dioxygenase	[EC:1.13.11.2]	Xenobiotics Biodegradation and Metabolism	0.000	9.68E-03	0.000	4
K00993	ethanolaminephosphotransferase	[EC:2.7.8.1]	Lipid Metabolism/ Metabolism of Other Amino Acids	0.000	3.30E-03	0.053	5
K03381	catechol 1,2-dioxygenase	[EC:1.13.11.1]	Xenobiotics Biodegradation and Metabolism	0.000	6.56E-03	0.000	5
K05784	benzoate 1,2-dioxygenase electron transfer component		Xenobiotics Biodegradation and Metabolism	0.086	6.30E-04	0.000	3
K03428	magnesium-protoporphyrin O-methyltransferase	[EC:2.1.1.11]	Metabolism of Cofactors and Vitamins	0.095	3.17E-03	0.100	3
K00320	coenzyme F420-dependent N5,N10-methylenetetrahydromethanopterin		Metabolism of Cofactors and Vitamins	0.133	2.33E-02	0.077	5
K01477	allantoicase	[EC:3.5.3.4]	Nucleotide Metabolism	0.141	4.96E-03	0.208	5
K00672	formylmethanofuran-tetrahydromethanopterin N-formyltransferase		Energy Metabolism/ Metabolism of Cofactors and Vitamins	0.149	2.66E-02	0.000	17
K07732	riboflavin kinase, archaea type	[EC:2.7.1.161]	Metabolism of Cofactors and Vitamins	0.353	2.02E-03	0.000	5
K00368	nitrite reductase (NO-forming)	[EC:1.7.2.1]	Energy Metabolism	0.491	7.78E-05	0.000	12
K01432	arylfornamidase	[EC:3.5.1.9]	Amino Acid Metabolism/ Carbohydrate Metabolism	0.237	7.53E-04	0.542	1
K01103	fructose-2,6-bisphosphatase	[EC:3.1.3.46]	Carbohydrate Metabolism	0.257	1.11E-03	0.841	1
K01612	4-hydroxybenzoate decarboxylase	[EC:4.1.1.61]	Xenobiotics Biodegradation and Metabolism	0.380	1.17E-02	0.214	2
K01833	trypanothione synthetase/amidase	[EC:6.3.1.9 3.5.1.-]	Metabolism of Other Amino Acids	0.000	4.13E-03	0.347	6
K07632	galactoside alpha-1,3-fucosyltransferase 4	[EC:2.4.1.-]	Signaling Molecules and Interaction/ Glycan Biosynthesis and Metabolism	0.000	2.15E-03	0.467	6
K11395	2-keto-3-deoxygluconate aldolase	[EC:4.1.2.-]	Carbohydrate Metabolism/ Metabolism	0.000	1.45E-01	0.284	55
K00148	glutathione-independent formaldehyde dehydrogenase	[EC:1.2.2.1.46]	Energy Metabolism	0.000	1.73E-03	0.503	6
K04509	formate dehydrogenase (cytochrome)	[EC:1.2.2.1]	Carbohydrate Metabolism	0.000	1.58E-03	0.261	20
K07544	benzylsuccinate CoA-transferase BbsF subunit	[EC:2.8.3.15]	Xenobiotics Biodegradation and Metabolism	0.000	1.02E-03	0.571	15
K00802	spermine synthase	[EC:2.5.1.22]	Amino Acid Metabolism/ Metabolism of Other Amino Acids	0.000	1.31E-03	0.268	4
K00295	methylenetetrahydrofolate dehydrogenase (NAD+)	[EC:1.5.1.15]	Metabolism of Cofactors and Vitamins	0.000	5.99E-05	0.667	8
K01907	acetoacetyl-CoA synthetase	[EC:6.2.1.16]	Carbohydrate Metabolism/ Lipid Metabolism	0.000	2.79E-04	0.633	8
K11517	(S)-2-hydroxy-acid oxidase	[EC:1.1.3.15]	Transport and Catabolism/ Carbohydrate Metabolism	0.000	1.35E-04	0.515	7
K00988	ATP adenyltransferase	[EC:2.7.7.53]	Nucleotide Metabolism	0.000	1.89E-03	0.276	16
K11204	glutamate-cysteine ligase catalytic subunit	[EC:6.3.2.2]	Metabolism of Other Amino Acids	0.000	1.37E-03	0.235	34
K02999	DNA-directed RNA polymerase I subunit A1	[EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.000	8.84E-05	0.664	34
K03004	DNA-directed RNA polymerase I subunit A43	[EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.000	8.84E-05	0.664	34
K03011	DNA-directed RNA polymerase II subunit C		Replication and Repair/Transcription/ Neurodegenerative Diseases	0.000	8.84E-05	0.664	34
K03016	DNA-directed RNA polymerase II subunit H		Replication and Repair/Transcription/ Neurodegenerative Diseases	0.000	8.84E-05	0.664	34
K03021	DNA-directed RNA polymerase III subunit C2	[EC:2.7.7.6]	Transcription/ Nucleotide Metabolism/Immune System	0.000	8.84E-05	0.664	34
K08049	adenylate cyclase 9	[EC:4.6.1.1]	Cell Communication/ Cell Growth and Death/ Signal Transduction	0.000	2.08E-04	0.939	32
K00234	succinate dehydrogenase (ubiquinone) flavoprotein subunit		Neurodegenerative Diseases/ Carbohydrate Metabolism/ Energy Metabolism	0.000	3.88E-04	0.612	28
K03002	DNA-directed RNA polymerase I subunit A2	[EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.000	8.84E-05	0.664	34
K03013	DNA-directed RNA polymerase II subunit E		Replication and Repair/Transcription/ Neurodegenerative Diseases	0.000	8.84E-05	0.664	34
K03027	DNA-directed RNA Polymerase III subunit C5	[EC:2.7.7.6]	Transcription/ Nucleotide Metabolism/Immune System	0.000	8.84E-05	0.664	34
K01490	AMP deaminase	[EC:3.5.4.6]	Nucleotide Metabolism	0.000	2.73E-02	0.305	8
K01511	ectonucleoside triphosphate diphosphohydrolase 5/6	[EC:3.6.1.6]	Nucleotide Metabolism	0.000	1.98E-03	0.377	8
K03766	beta-1,3-N-acetylglucosaminyltransferase 5	[EC:2.4.1.206]	Glycan Biosynthesis and Metabolism	0.000	1.64E-02	0.429	7
K03918	L-lysine 6-transaminase	[EC:2.6.1.36]	Amino Acid Metabolism	0.000	1.18E-02	0.253	8
K00718	galactoside 2-L-fucosyltransferase	[EC:2.4.1.69]	Glycan Biosynthesis and Metabolism	0.000	7.50E-03	0.464	8
K07819	beta-1,3-galactosyltransferase 1	[EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	0.000	3.70E-03	0.800	5
K07820	beta-1,3-galactosyltransferase 2	[EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	0.000	3.70E-03	0.800	5
K07508	acetyl-CoA acyltransferase 2	[EC:2.3.1.16]	Amino Acid Metabolism/ Lipid Metabolism/ Xenobiotics Biodegradation and Metabolism	0.000	1.85E-02	0.276	39
K00814	alanine transaminase	[EC:2.6.1.2]	Amino Acid Metabolism/ Energy Metabolism	0.000	2.66E-03	0.459	37
K03877	beta-1,3-galactosyltransferase 5	[EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	0.000	7.60E-03	0.429	7
K01900	succinyl-CoA synthetase beta subunit	[EC:6.2.1.4 6.2.1.5]	Carbohydrate Metabolism	0.000	2.18E-03	0.491	30
K11262	acetyl-CoA carboxylase [EC:6.4.1.2]		Carbohydrate Metabolism/ Lipid Metabolism/Endocrine System	0.000	3.09E-03	0.531	35
K00578	tetrahydromethanopterin S-methyltransferase subunit B	[EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.013	1.34E-03	0.364	5
K00582	tetrahydromethanopterin S-methyltransferase subunit F	[EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.059	1.34E-03	0.364	5
K03006	DNA-directed RNA polymerase II subunit A	[EC:2.7.7.6]	Replication and Repair/Transcription/ Neurodegenerative Diseases	0.062	8.84E-05	0.664	34
K00583	tetrahydromethanopterin S-methyltransferase subunit G	[EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.071	1.34E-03	0.364	5
K03050	DNA-directed RNA polymerase subunit E'	[EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.073	8.84E-05	0.664	34
K00201	formylmethanofuran dehydrogenase subunit B	[EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.084	3.39E-03	0.457	27
K11152	retinol dehydrogenase 11	[EC:1.1.1.-]	Metabolism of Cofactors and Vitamins	0.088	8.39E-04	0.530	8
K00579	tetrahydromethanopterin S-methyltransferase subunit C	[EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.092	1.34E-03	0.364	5
K00143	aminoadipate-semialdehyde dehydrogenase large subunit	[EC:1.2.1.31]	Amino Acid Metabolism	0.099	5.48E-03	0.556	7
K03045	DNA-directed RNA polymerase subunit B'	[EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.100	8.84E-05	0.664	34
K00202	formylmethanofuran dehydrogenase subunit C	[EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.103	3.39E-03	0.457	27
K00203	formylmethanofuran dehydrogenase subunit D	[EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.105	3.39E-03	0.457	27
K03056	DNA-directed RNA polymerase subunit L	[EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.108	8.84E-05	0.664	34
K09011	D-citramalate synthase	[EC:2.3.1.182]	Amino Acid Metabolism	0.109	2.44E-03	0.389	60
K03018	DNA-directed RNA polymerase III subunit C1	[EC:2.7.7.6]	Transcription/ Nucleotide Metabolism/Immune System	0.113	8.84E-05	0.664	34
K00167	2-oxoisovalerate dehydrogenase E1 component, beta subunit		Amino Acid Metabolism	0.119	2.24E-03	0.397	14
K00430	peroxidase [EC:1.11.1.7]		Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites/ Energy Metabolism	0.121	5.41E-03	0.408	12
K00580	tetrahydromethanopterin S-methyltransferase subunit D	[EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.121	1.34E-03	0.364	5
K00581	tetrahydromethanopterin S-methyltransferase subunit E	[EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.127	1.34E-03	0.364	5
K00400	methyl coenzyme M reductase system, component A2		Metabolism of Cofactors and Vitamins	0.129	7.18E-04	0.242	12
K00584	tetrahydromethanopterin S-methyltransferase subunit H	[EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.133	1.34E-03	0.364	5



K00200	formylmethanofuran dehydrogenase subunit A [EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.135	3.39E-03	0.457	27
K00204	formylmethanofuran dehydrogenase subunit H [EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.138	3.39E-03	0.457	27
K03058	DNA-directed RNA polymerase subunit N [EC:2.7.7.6]	Signal Transduction/Transcription/ Nucleotide M...	0.145	8.84E-05	0.664	34
K03047	DNA-directed RNA polymerase subunit D [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.146	8.84E-05	0.664	34
K00577	tetrahydromethanopterin S-methyltransferase subunit A [EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.149	1.34E-03	0.364	5
K00695	sucrose synthase [EC:2.4.1.13]	Carbohydrate Metabolism	0.152	2.58E-04	0.250	4
K02626	arginine decarboxylase [EC:4.1.1.19]	Amino Acid Metabolism	0.157	4.09E-04	0.333	3
K00187	2-oxoisovalerate ferredoxin oxidoreductase, beta subunit	Amino Acid Metabolism	0.161	5.63E-04	0.310	4
K00402	methyl-coenzyme M reductase gamma subunit [EC:2.8.4.1]	Metabolism of Cofactors and Vitamins	0.166	7.18E-04	0.242	12
K00150	glyceraldehyde-3-phosphate dehydrogenase (NAD(P)) [EC:1.2.1.59]	Carbohydrate Metabolism/ Energy Metabolism	0.168	8.67E-04	0.647	14
K00399	methyl-coenzyme M reductase alpha subunit [EC:2.8.4.1]	Metabolism of Cofactors and Vitamins	0.169	7.18E-04	0.242	12
K01592	tyrosine decarboxylase [EC:4.1.1.25]	Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites	0.169	1.35E-03	0.558	10
K00125	formate dehydrogenase, beta subunit [EC:1.2.1.2]	Carbohydrate Metabolism/ Energy Metabolism	0.173	4.05E-03	0.247	38
K03421	methyl-coenzyme M reductase subunit C	Metabolism of Cofactors and Vitamins	0.175	7.18E-04	0.242	12
K03055	DNA-directed RNA polymerase subunit K [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.176	8.84E-05	0.664	34
K03049	DNA-directed RNA polymerase subunit E [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.181	8.84E-05	0.664	34
K11260	formylmethanofuran dehydrogenase subunit G [EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.185	3.39E-03	0.457	27
K00293	saccharopine dehydrogenase (NADP+, L-glutamate forming)	Amino Acid Metabolism	0.212	1.27E-03	0.600	6
K03422	methyl-coenzyme M reductase subunit D	Metabolism of Cofactors and Vitamins	0.215	7.18E-04	0.242	12
K03044	DNA-directed RNA polymerase subunit B [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.218	8.84E-05	0.664	34
K01568	pyruvate decarboxylase [EC:4.1.1.1]	Carbohydrate Metabolism	0.222	2.84E-02	0.366	45
K00189	2-oxoisovalerate ferredoxin oxidoreductase, gamma subunit	Amino Acid Metabolism	0.223	5.63E-04	0.310	4
K00401	methyl-coenzyme M reductase beta subunit [EC:2.8.4.1]	Metabolism of Cofactors and Vitamins	0.224	7.18E-04	0.242	12
K00007	D-arabinitol 4-dehydrogenase [EC:1.1.1.11]	Carbohydrate Metabolism	0.237	1.53E-03	0.292	11
K03042	DNA-directed RNA polymerase subunit A' [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.245	8.84E-05	0.664	34
K01573	oxaloacetate decarboxylase, gamma subunit [EC:4.1.1.3]	Amino Acid Metabolism/ Carbohydrate Metabolism	0.245	2.01E-03	0.347	21
K03041	DNA-directed RNA polymerase subunit A [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.253	8.84E-05	0.664	34
K11261	formylmethanofuran dehydrogenase subunit E [EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.259	3.39E-03	0.457	27
K03051	DNA-directed RNA polymerase subunit F [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.272	8.84E-05	0.664	34
K10251	beta-keto reductase [EC:1.1.1.-]	Lipid Metabolism	0.330	5.24E-03	0.382	13
K00828	serine-glyoxylate transaminase [EC:2.6.1.45]	Amino Acid Metabolism	0.361	4.12E-03	0.220	24
K00552	glycine N-methyltransferase [EC:2.1.1.20]	Amino Acid Metabolism	0.367	5.13E-03	0.325	20
K07512	mitochondrial trans-2-enoyl-CoA reductase [EC:1.3.1.38]	Lipid Metabolism	0.382	3.71E-03	0.455	7
K00139	succinate-semialdehyde dehydrogenase [EC:1.2.1.24]	Amino Acid Metabolism/ Carbohydrate Metabolism	0.410	2.67E-03	0.609	23
K00196	carbon-monoxide dehydrogenase iron sulfur subunit	Energy Metabolism/ Xenobiotics Biodegradation and Metabolism	0.419	1.90E-04	0.395	26
K01769	guanylate cyclase, other [EC:4.6.1.2]	Nucleotide Metabolism	0.429	2.06E-04	0.938	31
K00392	sulfite reductase (ferredoxin) [EC:1.8.7.1]	Energy Metabolism/ Metabolism of Other Amino Acids	0.431	3.76E-04	0.232	5
K06208	chorismate mutase [EC:5.4.99.5]	Amino Acid Metabolism	0.442	4.77E-03	0.544	14
K00032	phosphogluconate 2-dehydrogenase [EC:1.1.1.43]	Carbohydrate Metabolism/ Metabolism of Other Amino Acids	0.472	1.03E-03	0.278	10
K11473	glycolate oxidase iron-sulfur subunit	Carbohydrate Metabolism	0.496	1.35E-04	0.515	7

**Table S2C. IBD-enriched enzymes**

ID	Name	Functional Class	OR - IBD	Centrality Score	Clustering Coefficient	In-degree
K00450	gentisate 1,2-dioxygenase [EC:1.13.11.4]	Amino Acid Metabolism	Inf	0.00E+00	0.000	1
K00423	L-ascorbate oxidase [EC:1.10.3.3]	Carbohydrate Metabolism	Inf	0.00E+00	0.000	1
K00499	choline monooxygenase [EC:1.14.15.7]	Amino Acid Metabolism	Inf	5.40E-07	0.000	2
K05973	poly(3-hydroxybutyrate) depolymerase [EC:3.1.1.75]	Carbohydrate Metabolism	Inf	0.00E+00	0.000	1
K00258	NONE	Biosynthesis of Polyketides and Terpenoids/ Xenobiotics Biodegradation and Metabolism	25.017	0.00E+00	0.000	1
K11440	choline dehydrogenase [EC:1.1.1.1]	Amino Acid Metabolism	11.108	5.40E-07	0.000	2
K10984	PTS system, galactosamine-specific IIB component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	7.504	0.00E+00	0.000	0
K10986	PTS system, galactosamine-specific IID component	Membrane Transport/ Carbohydrate Metabolism	7.490	0.00E+00	0.000	0
K08347	nitrate reductase 2, gamma subunit [EC:1.7.99.4]	Energy Metabolism	6.288	0.00E+00	0.000	0
K02301	protoheme IX farnesyltransferase [EC:2.5.1.-]	Energy Metabolism/ Metabolism of Cofactors and Vitamins	5.776	0.00E+00	0.000	1
K00816	kynurenine-oxoglutarate transaminase [EC:2.6.1.7]	Amino Acid Metabolism	5.673	0.00E+00	0.000	1
K02812	PTS system, sorbose-specific IIA component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	5.242	0.00E+00	0.000	0
K01061	carboxymethylenebutenolidase [EC:3.1.1.45]	Xenobiotics Biodegradation and Metabolism	4.957	0.00E+00	0.000	2
K01757	strictosidine synthase [EC:4.3.3.2]	Biosynthesis of Other Secondary Metabolites	4.751	0.00E+00	0.000	1
K11337	3-hydroxyethyl bacteriochlorophyllide a dehydrogenase [EC:1.-.-.-]	Metabolism of Cofactors and Vitamins	4.584	0.00E+00	0.000	0
K08345	nitrate reductase 2, alpha subunit [EC:1.7.99.4]	Energy Metabolism	3.893	0.00E+00	0.000	0
K08346	nitrate reductase 2, beta subunit [EC:1.7.99.4]	Energy Metabolism	3.806	0.00E+00	0.000	0
K00108	choline dehydrogenase [EC:1.1.99.1]	Amino Acid Metabolism	3.586	5.40E-07	0.000	2
K07635	galactoside alpha-1,3-fucosyltransferase 7 [EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	3.577	0.00E+00	0.000	1
K05712	3-[3-hydroxy-phenyl]propanate hydroxylase [EC:1.14.13.-]	Amino Acid Metabolism	3.259	0.00E+00	0.000	0
K08726	soluble epoxide hydrolase [EC:3.3.2.10]	Transport and Catabolism/ Lipid Metabolism/ Xenobiotics Biodegradation and Metabolism	3.150	0.00E+00	0.000	0
K02813	PTS system, sorbose-specific IIB component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	3.035	0.00E+00	0.000	0
K05286	phosphatidylinositol glycan, class B [EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	2.994	1.62E-06	0.000	1
K00216	2,3-dihydro-2,3-dihydroxybenzoate dehydrogenase [EC:1.3.1.28]	Biosynthesis of Polyketides and Terpenoids	2.631	0.00E+00	0.000	2
K08092	3-dehydro-L-gulonate 2-dehydrogenase [EC:1.1.1.130]	Carbohydrate Metabolism	2.552	0.00E+00	0.000	0
K08361	nitrate reductase 2, delta subunit [EC:1.7.99.4]	Energy Metabolism	2.519	0.00E+00	0.000	0
K02746	PTS system, N-acetylgalactosamine-specific IIC component	Membrane Transport/ Carbohydrate Metabolism	2.373	0.00E+00	0.000	0
K02786	PTS system, lactose-specific IIA component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	2.208	0.00E+00	0.000	0
K03400	long-chain-fatty-acyl-CoA reductase [EC:1.2.1.50]	Metabolism	2.178	1.78E-05	0.000	1
K00369	nitrate reductase [EC:1.7.99.4]	Energy Metabolism	2.152	0.00E+00	0.000	0
K00372	nitrate reductase catalytic subunit [EC:1.7.99.4]	Energy Metabolism	2.147	0.00E+00	0.000	0
K02787	PTS system, lactose-specific IIB component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	2.038	0.00E+00	0.000	0
K05368	aquacobalamin reductase / NAD(P)H-flavin reductase [EC:1.16.1.3]	Metabolism of Cofactors and Vitamins	Inf	0.00E+00	0.000	3
K06132	putative cardiolipin synthase [EC:2.7.8.-]	Lipid Metabolism	11.833	0.00E+00	0.000	3
K00363	nitrite reductase (NAD(P)H) small subunit [EC:1.7.1.4]	Energy Metabolism	4.789	0.00E+00	0.000	12
K00299	FMN reductase [EC:1.5.1.29]	Metabolism	2.949	0.00E+00	0.000	3
K00508	linoleoyl-CoA desaturase [EC:1.14.19.3]	Lipid Metabolism	28.168	0.00E+00	0.500	2
K04104	NONE	Xenobiotics Biodegradation and Metabolism	8.242	0.00E+00	0.400	0
K02819	PTS system, trehalose-specific IIC component	Membrane Transport/ Carbohydrate Metabolism	5.506	1.37E-06	0.417	2
K05831	acetyl-lysine deacetylase [EC:3.5.1.1]	Amino Acid Metabolism	3.628	0.00E+00	0.333	0
K03366	acetoin dehydrogenase [EC:1.1.1.5]	Carbohydrate Metabolism	2.461	0.00E+00	0.500	1
K02818	PTS system, trehalose-specific IIB component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	2.459	1.37E-06	0.417	2
K09883	cobaltochelatase CobT [EC:6.6.1.2]	Metabolism of Cofactors and Vitamins	2.333	0.00E+00	0.500	1
K08679	UDP-glucuronate 4-epimerase [EC:5.1.3.6]	Carbohydrate Metabolism	2.234	0.00E+00	0.250	1
K00073	ureidoglycolate dehydrogenase [EC:1.1.1.154]	Nucleotide Metabolism	2.217	0.00E+00	1.000	2
K02817	PTS system, trehalose-specific IIA component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	2.168	1.37E-06	0.417	2
K02744	PTS system, N-acetylgalactosamine-specific IIA component	Membrane Transport/ Carbohydrate Metabolism	2.090	0.00E+00	0.500	0
K05551	3-oxoacyl-ACP synthase I [EC:2.3.1.-]	Biosynthesis of Polyketides and Terpenoids/ Lipid Metabolism	Inf	0.00E+00	0.522	44
K01608	tartronate-semialdehyde synthase [EC:4.1.1.47]	Carbohydrate Metabolism	5.641	3.84E-05	0.438	16
K11154	retinol dehydrogenase 16 [EC:1.1.1.-]	Metabolism of Cofactors and Vitamins	3.495	0.00E+00	0.700	7
K01674	carbonic anhydrase [EC:4.2.1.1]	Energy Metabolism	2.776	0.00E+00	0.377	25
K00932	propionate kinase [EC:2.7.2.15]	Carbohydrate Metabolism	2.621	0.00E+00	1.000	6
K01475	NONE	Amino Acid Metabolism/ Nucleotide Metabolism/ Xenobiotics Biodegradation and Metabolism	2.467	0.00E+00	0.889	10
K01718	pseudouridylate synthase [EC:4.2.1.70]	Nucleotide Metabolism	2.419	0.00E+00	0.569	9
K04568	lysyl-tRNA synthetase, class II [EC:6.1.1.6]	Translation	2.252	0.00E+00	0.600	5
K06127	ubiquinone biosynthesis methyltransferase [EC:2.1.1.-]	Metabolism of Cofactors and Vitamins	Inf	1.07E-03	0.000	1
K10764	O-succinylhomoserine sulphydrylase [EC:2.5.1.-]	Amino Acid Metabolism	Inf	1.33E-04	0.000	1
K01484	succinylarginine dihydrolase [EC:3.5.3.23]	Amino Acid Metabolism	7.127	4.23E-03	0.000	1
K03185	2-octaprenyl-6-methoxyphenol hydroxylase [EC:1.14.13.-]	Metabolism of Cofactors and Vitamins	5.192	3.09E-03	0.000	1
K03184	2-octaprenyl-3-methyl-6-methoxy-1,4-benzoquinol hydroxylase	Metabolism of Cofactors and Vitamins	4.887	9.02E-03	0.000	2
K07251	thiamine kinase [EC:2.7.1.89]	Metabolism of Cofactors and Vitamins	3.737	5.45E-05	0.000	1
K01521	CDP-diacylglycerol pyrophosphatase [EC:3.6.1.26]	Lipid Metabolism	3.597	9.61E-04	0.000	1

K00103	L-gulonolactone oxidase [EC:1.1.3.8]	Carbohydrate Metabolism	3.391	5.21E-03	0.000	1
K03119	taurine dioxygenase [EC:1.14.11.17]	Metabolism of Other Amino Acids	3.090	4.67E-03	0.167	2
K05939	acyl-[acyl-carrier-protein]-phospholipid O-acyltransferase /	Lipid Metabolism	3.075	1.15E-03	0.054	1
K00231	protoporphyrinogen oxidase [EC:1.3.3.4]	Metabolism of Cofactors and Vitamins	2.925	4.73E-03	0.000	2
K05713	2,3-dihydroxyphenylpropionate 1,2-dioxygenase [EC:1.13.11.16]	Amino Acid Metabolism	2.642	7.78E-03	0.000	2
K06447	succinylglutamic semialdehyde dehydrogenase [EC:1.2.1.71]	Amino Acid Metabolism	2.481	4.36E-03	0.000	1
K02549	O-succinylbenzoate synthase [EC:4.2.1.113]	Metabolism of Cofactors and Vitamins	2.358	2.09E-03	0.000	1
K00119	NONE	Biosynthesis of Polyketides and Terpenoids/ Metabolism of Other Amino Acids/ Xenobiotics	2.309	1.17E-03	0.167	2
K07542	phosphatidylinositol glycan, class V [EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	2.198	1.05E-03	0.000	1
K00840	succinylornithine aminotransferase [EC:2.6.1.81]	Amino Acid Metabolism	2.045	4.30E-03	0.000	1
K00465	NONE	Xenobiotics Biodegradation and Metabolism	Inf	1.91E-03	0.107	6
K00720	ceramide glucosyltransferase [EC:2.4.1.80]	Glycan Biosynthesis and Metabolism/ Lipid Metabolism	7.861	1.05E-03	0.000	4
K08723	5-nucleotidase [EC:3.1.3.5]	Metabolism of Cofactors and Vitamins/ Nucleotide Metabolism	5.403	1.62E-02	0.192	52
K02554	2-keto-4-pentenote hydratase [EC:4.2.1.80]	Amino Acid Metabolism/ Xenobiotics Biodegradation and Metabolism	5.395	4.55E-03	0.000	3
K02079	N-acetylgalactosamine-6-phosphate deacetylase [EC:3.5.1.25]	Carbohydrate Metabolism	4.256	3.33E-03	0.050	4
K00480	salicylate hydroxylase [EC:1.14.13.1]	Xenobiotics Biodegradation and Metabolism	4.196	5.33E-03	0.033	4
K03788	acid phosphatase (class B) [EC:3.1.3.2]	Metabolism of Cofactors and Vitamins/ Xenobiotics Biodegradation and Metabolism	3.618	2.28E-03	0.000	3
K01047	phospholipase A2 [EC:3.1.1.4]	Signal Transduction/ Lipid Metabolism/ Circulatory System	3.189	6.67E-03	0.115	5
K01825	3-hydroxyacyl-CoA dehydrogenase / enoyl-CoA hydratase /	Amino Acid Metabolism/ Biosynthesis of Polyketides and Terpenoids/ Carbohydrate Metabolism	2.861	1.30E-02	0.203	32
K00261	glutamate dehydrogenase (NAD(P)+) [EC:1.4.1.3]	Amino Acid Metabolism/ Energy Metabolism/ Metabolism of Other Amino Acids	2.653	1.59E-02	0.208	48
K01782	3-hydroxyacyl-CoA dehydrogenase / enoyl-CoA hydratase /	Amino Acid Metabolism/ Biosynthesis of Polyketides and Terpenoids/ Carbohydrate Metabolism	2.633	1.30E-02	0.203	32
K00260	glutamate dehydrogenase [EC:1.4.1.2]	Amino Acid Metabolism/ Energy Metabolism	2.309	1.59E-02	0.208	48
K09251	putrescine aminotransferase [EC:2.6.1.82]	Amino Acid Metabolism	2.223	1.26E-03	0.189	3
K00094	galactitol-1-phosphate 5-dehydrogenase [EC:1.1.1.251]	Carbohydrate Metabolism	2.168	3.33E-03	0.100	3
K00383	glutathione reductase (NADPH) [EC:1.8.1.7]	Metabolism of Other Amino Acids	2.140	1.62E-02	0.203	5
K01856	muconate cycloisomerase [EC:5.5.1.1]	Xenobiotics Biodegradation and Metabolism	2.120	5.49E-03	0.000	4
K09473	gamma-glutamyl-gamma-aminobutyrate hydrolase [EC:3.5.1.94]	Amino Acid Metabolism/ Enzyme Families	5.428	3.32E-03	0.300	1
K00137	aminobutyraldehyde dehydrogenase [EC:1.2.1.19]	Amino Acid Metabolism/ Metabolism of Other Amino Acids	4.504	7.33E-04	0.367	2
K01561	haloacetate dehalogenase [EC:3.8.1.3]	Xenobiotics Biodegradation and Metabolism	3.877	1.93E-04	0.639	1
K03081	3-dehydro-L-gulonate-6-phosphate decarboxylase [EC:4.1.1.85]	Carbohydrate Metabolism	3.856	2.77E-03	0.500	2
K05526	succinylglutamate desuccinylase [EC:3.5.1.96]	Amino Acid Metabolism	3.613	4.43E-03	0.401	1
K09699	2-oxoisovalerate dehydrogenase E2 component (dihydropyridol)	Amino Acid Metabolism	3.075	3.88E-04	0.250	2
K07751	PeptB aminopeptidase [EC:3.4.11.23]	Enzyme Families/ Metabolism of Other Amino Acids	2.036	9.70E-04	0.217	1
K04782	isochorismate pyruvate-lyase [EC:4.1.3.-]	Biosynthesis of Polyketides and Terpenoids	Inf	2.24E-04	0.400	3
K00467	lactate 2-monoxygenase [EC:1.13.12.4]	Carbohydrate Metabolism	Inf	1.32E-04	0.607	3
K05301	sulfite dehydrogenase [EC:1.8.2.1]	Energy Metabolism	Inf	4.81E-05	0.357	5
K00209	enoyl-[acyl-carrier-protein] reductase (NADPH2, B-specific)	Metabolism	Inf	4.60E-05	0.929	5
K01948	carbamoyl-phosphate synthase (ammonia) [EC:6.3.4.16]	Amino Acid Metabolism/ Energy Metabolism/ Enzyme Families	Inf	9.88E-04	0.328	28
K07544	benzylsuccinate CoA-transferase BbsF subunit [EC:2.8.3.15]	Xenobiotics Biodegradation and Metabolism	56.865	1.02E-03	0.571	15
K00838	aromatic amino acid aminotransferase I [EC:2.6.1.57]	Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites	40.614	2.82E-02	0.300	20
K00148	glutathione-independent formaldehyde dehydrogenase [EC:1.2.1.46]	Energy Metabolism	23.521	1.73E-03	0.503	6
K01252	enterobactin isochorismatase [EC:3.3.2.1]	Biosynthesis of Polyketides and Terpenoids	19.209	5.22E-04	0.500	3
K06116	glycerol 3-phosphatase 1 [EC:3.1.3.21]	Lipid Metabolism	15.816	1.37E-03	0.363	7
K11395	2-keto-3-deoxy-glucuronate aldolase [EC:4.1.2.-]	Carbohydrate Metabolism/ Metabolism	13.082	1.45E-01	0.284	55
K01029	3-oxoacid CoA-transferase subunit B [EC:2.8.3.5]	Amino Acid Metabolism/ Carbohydrate Metabolism/ Lipid Metabolism	11.208	4.70E-04	0.595	14
K00246	fumarate reductase subunit C [EC:1.3.99.1]	Signal Transduction/ Carbohydrate Metabolism/ Energy Metabolism	7.816	3.88E-04	0.612	28
K01593	aromatic-L-amino-acid decarboxylase [EC:4.1.1.28]	Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites	7.772	8.31E-03	0.217	20
K00158	pyruvate oxidase [EC:1.2.3.3]	Carbohydrate Metabolism	7.431	4.39E-03	0.535	35
K00242	succinate dehydrogenase hydrophobic membrane anchor protein	Carbohydrate Metabolism/ Energy Metabolism/ Xenobiotics Biodegradation and Metabolism	6.803	3.88E-04	0.612	28
K04509	formate dehydrogenase (cytochrome) [EC:1.2.2.1]	Carbohydrate Metabolism	6.239	1.58E-03	0.261	20
K00116	malate dehydrogenase (quinone) [EC:1.1.5.4]	Carbohydrate Metabolism	6.141	1.73E-03	0.477	27
K02560	lipid A biosynthesis (KDO)2-(lauroyl)-lipid iya acyltransferase	Glycan Biosynthesis and Metabolism	6.041	3.24E-04	0.446	5
K00673	arginine N-succinyltransferase [EC:2.3.1.109]	Amino Acid Metabolism	5.898	4.16E-03	0.333	3
K00892	inosine kinase [EC:2.7.1.73]	Nucleotide Metabolism	5.740	4.26E-03	0.422	23
K01637	isocitrate lyase [EC:4.1.3.1]	Carbohydrate Metabolism	5.305	2.65E-03	0.410	4
K00247	fumarate reductase subunit D [EC:1.3.99.1]	Signal Transduction/ Carbohydrate Metabolism/ Energy Metabolism	5.212	3.88E-04	0.612	28
K11472	glycolate oxidase FAD binding subunit	Carbohydrate Metabolism	5.066	1.35E-04	0.515	7
K11196	PTS system, fructose-specific IIC component	Membrane Transport/ Carbohydrate Metabolism	5.066	9.91E-04	0.900	5
K03821	polyhydroxyalkanoate synthase [EC:2.3.1.-]	Carbohydrate Metabolism	4.953	2.15E-03	0.600	5
K03782	catalase/peroxidase [EC:1.11.1.6]	Amino Acid Metabolism/ Energy Metabolism	4.337	1.18E-04	0.267	3
K01595	phosphoenolpyruvate carboxylase [EC:4.1.1.31]	Carbohydrate Metabolism/ Energy Metabolism	4.263	5.57E-03	0.292	31
K01085	glucose-1-phosphatase [EC:3.1.3.10]	Carbohydrate Metabolism	4.236	5.74E-03	0.471	9
K01682	aconitate hydratase 2 [EC:4.2.1.3]	Carbohydrate Metabolism/ Energy Metabolism	4.182	5.50E-04	0.357	4
K11147	dehydrogenase/reductase SDR family member 4 [EC:1.1.-.-]	Transport and Catabolism/ Metabolism of Cofactors and Vitamins	4.127	5.30E-04	0.627	8
K01638	malate synthase [EC:2.3.3.9]	Carbohydrate Metabolism	3.938	1.79E-02	0.310	55
K02802	PTS system, N-acetylglucosamine-specific IIA component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	3.807	1.98E-03	0.333	4
K08350	formate dehydrogenase-N, gamma subunit [EC:1.2.1.2]	Signal Transduction/ Carbohydrate Metabolism/ Energy Metabolism	3.791	4.05E-03	0.247	38
K11263	acetyl/propionyl carboxylase subunit alpha	Lipid Metabolism	3.642	3.09E-03	0.531	35
K00153	glycine oxidase [EC:1.4.3.19]	Metabolism of Cofactors and Vitamins	3.601	1.65E-04	0.363	18
K07632	galactoside alpha-1,3-fucosyltransferase 4 [EC:2.4.1.-]	Signaling Molecules and Interaction/ Glycan Biosynthesis and Metabolism	3.577	2.15E-03	0.467	6
K00291	saccharopine dehydrogenase (NADP+, L-lysine forming) [EC:1.5.1.8]	Amino Acid Metabolism	3.470	7.71E-05	0.309	5
K03181	chorismate--pyruvate lyase [EC:4.1.3.40]	Metabolism of Cofactors and Vitamins	3.451	4.87E-03	0.303	15
K00631	glycerol-3-phosphate O-acyltransferase [EC:2.3.1.15]	Lipid Metabolism	3.358	7.09E-03	0.536	7
K01483	ureidoglycolate hydrolase [EC:3.5.3.19]	Nucleotide Metabolism	3.326	2.16E-02	0.222	49
K03472	D-erythrose 4-phosphate dehydrogenase [EC:1.2.1.72]	Metabolism of Cofactors and Vitamins	3.266	1.95E-03	0.452	4
K00167	2-oxoisovalerate dehydrogenase E1 component, beta subunit	Amino Acid Metabolism	3.201	2.24E-03	0.397	14
K08348	formate dehydrogenase-N, alpha subunit [EC:1.2.1.2]	Signal Transduction/ Carbohydrate Metabolism/ Energy Metabolism	3.167	4.05E-03	0.247	38
K11178	xanthine dehydrogenase YagS FAD-binding subunit [EC:1.17.1.4]	Nucleotide Metabolism	3.147	6.95E-04	0.615	11
K10213	ribosylpyrimidine nucleosidase [EC:3.2.2.8]	Nucleotide Metabolism	3.144	1.79E-04	0.773	8
K03897	lysine N6-hydroxylase [EC:1.14.13.59]	Amino Acid Metabolism	3.057	1.04E-03	0.400	5
K00056	tartrate dehydrogenase [EC:1.1.1.93]	Carbohydrate Metabolism	3.036	1.01E-03	0.333	4
K01087	trehalose-phosphatase [EC:3.1.3.12]	Carbohydrate Metabolism	3.029	4.13E-03	0.250	7
K05851	adenylate cyclase, class I [EC:4.6.1.1]	Infectious Diseases/ Nucleotide Metabolism	3.008	2.08E-04	0.939	32
K01524	guanosine-5-triphosphate-3-diphosphate pyrophosphatase	Nucleotide Metabolism	2.986	1.11E-03	0.333	4
K01240	uridine nucleosidase [EC:3.2.2.3]	Nucleotide Metabolism	2.983	1.40E-04	0.544	6
K00049	glyoxylate reductase (NADP+) [EC:1.1.1.79]	Carbohydrate Metabolism	2.838	1.19E-02	0.217	29
K00665	fatty acid synthase, animal type [EC:2.3.1.85]	Lipid Metabolism/Endocrine System	2.716	2.72E-02	0.351	46
K01965	propionyl-CoA carboxylase alpha chain [EC:6.4.1.3]	Amino Acid Metabolism/ Carbohydrate Metabolism	2.673	5.28E-04	0.608	17
K05921	5-oxopent-3-ene-1,2,5-tricarboxylate decarboxylase /	Amino Acid Metabolism	2.640	2.11E-03	0.333	3
K04781	salicylate synthetase [EC:5.4.4.2.4.1.3.-]	Biosynthesis of Polyketides and Terpenoids	2.615	5.87E-03	0.345	10
K01505	1-aminocyclopropane-1-carboxylate deaminase [EC:3.5.99.7]	Carbohydrate Metabolism	2.536	1.92E-03	0.455	11
K06445	acyl-CoA dehydrogenase [EC:1.3.99.-]	Lipid Metabolism	2.518	7.97E-04	0.478	13
K01833	trypanothione synthetase/amidase [EC:6.3.1.9.3.5.1.-]	Metabolism of Other Amino Acids	2.516	4.13E-03	0.347	6
K00117	quinoprotein glucose dehydrogenase [EC:1.1.5.2]	Carbohydrate Metabolism	2.488	9.26E-03	0.319	12
K01690	phosphogluconate dehydratase [EC:4.2.1.12]	Carbohydrate Metabolism	2.481	2.39E-03	0.333	3
K01584	arginine decarboxylase [EC:4.1.1.19]	Amino Acid Metabolism	2.462	4.09E-04	0.333	3
K00958	sulfate adenyltransferase [EC:2.7.7.4]	Energy Metabolism/ Metabolism of Other Amino Acids/ Nucleotide Metabolism	2.442	2.14E-03	0.411	4
K03777	D-lactate dehydrogenase [EC:1.1.1.28]	Carbohydrate Metabolism	2.436	8.83E-04	0.509	35
K05351	D-xylulose reductase [EC:1.1.1.9]	Carbohydrate Metabolism	2.370	3.53E-04	0.500	5
K00163	pyruvate dehydrogenase E1 component [EC:1.2.4.1]	Amino Acid Metabolism/ Carbohydrate Metabolism	2.344	2.66E-03	0.452	46
K03520	carbon-monoxide dehydrogenase large subunit [EC:1.2.99.2]	Energy Metabolism/ Xenobiotics Biodegradation and Metabolism	2.209	1.90E-04	0.395	26
K06120	glycerol dehydratase large subunit [EC:4.2.1.30]	Lipid Metabolism	2.155	3.09E-04	0.583	8
K04092	chorismate mutase [EC:5.4.99.5]	Amino Acid Metabolism	2.106	4.77E-03	0.544	14
K09698	nondiscriminating glutamyl-tRNA synthetase [EC:6.1.1.24]	Translation	2.098	1.41E-02	0.418	19
K00692	levansucrase [EC:2.4.1.10]	Signal Transduction/ Carbohydrate Metabolism	2.064	2.27E-03	0.340	6
K00121	5-(hydroxymethyl)glutathione dehydrogenase / alcohol dehydrogenase	Amino Acid Metabolism/ Carbohydrate Metabolism/ Energy Metabolism/ Lipid Metabolism	2.058	1.15E-02	0.320	25
K01040	glutathione CoA-transferase, subunit B [EC:2.8.3.12]	Carbohydrate Metabolism/ Xenobiotics Biodegradation and Metabolism	2.040	9.40E-04	0.403	4
K06121	glycerol dehydratase medium subunit [EC:4.2.1.30]	Lipid Metabolism	2.023	3.09E-04	0.583	8



K00101	L-lactate dehydrogenase (cytochrome) [EC:1.1.2.3]	Carbohydrate Metabolism	2.015	1.57E-04	0.596	3
K01942	biotin-protein ligase [EC:6.3.4.9 6.3.4.10 6.3.4.11 6.3.4.15]	Metabolism of Cofactors and Vitamins	2.005	1.24E-03	0.618	3

**Table S2D. IBD-depleted enzymes**

ID	Name	Functional Class	OR - IBD	Centrality Score	Clustering Coefficient	In-degree
K03862	vanillate monoxygenase [EC:1.14.13.82]	Xenobiotics Biodegradation and Metabolism	0.000	0.00E+00	0.167	0
K00888	phosphatidylinositol 4-kinase [EC:2.7.1.67]	Signal Transduction/ Carbohydrate Metabolism	0.000	0.00E+00	0.000	0
K00902	dolichol kinase [EC:2.7.1.108]	Glycan Biosynthesis and Metabolism	0.000	0.00E+00	0.000	0
K01106	inositol 1,4,5-trisphosphate 5-phosphatase [EC:3.1.3.56]	Signal Transduction/ Carbohydrate Metabolism	0.000	0.00E+00	0.000	2
K01233	chitosanase [EC:3.2.1.132]	Carbohydrate Metabolism	0.000	0.00E+00	0.000	1
K03852	sulfoacetaldehyde acetyltransferase [EC:2.3.3.15]	Metabolism of Other Amino Acids	0.000	0.00E+00	0.189	0
K03863	vanillate monoxygenase [EC:1.14.13.82]	Xenobiotics Biodegradation and Metabolism	0.000	0.00E+00	0.167	0
K08686	2-chlorobenzoate 1,2-dioxygenase [EC:1.14.12.13]	Xenobiotics Biodegradation and Metabolism	0.000	0.00E+00	0.000	0
K09881	acylglycerol kinase [EC:2.7.1.94]	Lipid Metabolism	0.000	2.70E-05	0.000	1
K10572	inositol-pentakisphosphate 2-kinase [EC:2.7.1.158]	Signal Transduction/ Carbohydrate Metabolism	0.000	0.00E+00	0.000	0
K05300	NONE	Xenobiotics Biodegradation and Metabolism	0.000	0.00E+00	0.000	0
K05356	trans-octaprenyltranstransferase [EC:2.5.1.11]	Biosynthesis of Polyketides and Terpenoids	0.033	1.62E-06	0.000	1
K05710	ferredoxin subunit of phenylpropionate dioxygenase	Amino Acid Metabolism	0.072	0.00E+00	0.000	0
K04102	4,5-dihydroxyphthalate decarboxylase [EC:4.1.1.55]	Xenobiotics Biodegradation and Metabolism	0.243	0.00E+00	0.167	0
K04107	4-hydroxybenzoyl-CoA reductase subunit 1 [EC:1.3.99.20]	Xenobiotics Biodegradation and Metabolism	0.305	0.00E+00	0.000	0
K02753	PTS system, arbutin-, cellobiose-, and salicin-specific IIC	Membrane Transport/ Carbohydrate Metabolism	0.314	0.00E+00	0.000	0
K04708	3-dehydroshinganine reductase [EC:1.1.1.102]	Lipid Metabolism	0.335	0.00E+00	0.000	0
K01617	4-oxalocrotonate decarboxylase [EC:4.1.1.77]	Xenobiotics Biodegradation and Metabolism	0.390	5.84E-06	0.000	1
K01110	phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase [EC:3.1.3.67]	Cell Communication/ Cell Growth and Death/ Signal Transduction	0.428	0.00E+00	0.000	0
K05363	serine/alanine adding enzyme [EC:2.3.2.10]	Glycan Biosynthesis and Metabolism	0.429	0.00E+00	0.000	1
K04103	indolepyruvate decarboxylase [EC:4.1.1.74]	Amino Acid Metabolism	0.430	0.00E+00	0.000	0
K01001	UDP-N-acetylglucosamine-dolichyl-phosphate	Glycan Biosynthesis and Metabolism	0.457	1.62E-06	0.000	1
K03330	glutamyl-tRNA(Gln) amidotransferase subunit E [EC:6.3.5.7]	Translation	0.465	0.00E+00	0.000	1
K01117	sphingomyelin phosphodiesterase [EC:3.1.4.12]	Lipid Metabolism	0.467	0.00E+00	0.000	0
K05797	4-cresol dehydrogenase (hydroxylating) [EC:1.17.99.1]	Xenobiotics Biodegradation and Metabolism	0.492	0.00E+00	0.000	1
K05296	3(or 17)beta-hydroxysteroid dehydrogenase [EC:1.1.1.51]	Lipid Metabolism	0.000	1.65E-05	0.200	5
K00514	zeta-carotene desaturase [EC:1.14.99.30]	Biosynthesis of Polyketides and Terpenoids	0.000	0.00E+00	1.000	2
K08233	polyneuridine-aldehyde esterase [EC:3.1.1.78]	Biosynthesis of Other Secondary Metabolites	0.000	0.00E+00	0.550	0
K10207	testosterone 17beta-dehydrogenase (NADP+) [EC:1.1.1.64]	Lipid Metabolism	0.000	0.00E+00	0.833	2
K00315	dimethylglycine dehydrogenase [EC:1.5.99.2]	Amino Acid Metabolism	0.000	0.00E+00	0.400	0
K00071	11beta-hydroxysteroid dehydrogenase [EC:1.1.1.146]	Lipid Metabolism/Excretory System	0.053	6.89E-06	0.333	2
K06151	glucuronate 2-dehydrogenase alpha chain [EC:1.1.99.3]	Carbohydrate Metabolism	0.055	0.00E+00	0.500	2
K00039	ribitol 2-dehydrogenase [EC:1.1.1.56]	Carbohydrate Metabolism	0.268	0.00E+00	1.000	2
K01075	4-hydroxybenzoyl-CoA thioesterase [EC:3.1.2.23]	Metabolism of Cofactors and Vitamins/ Xenobiotics Biodegradation and Metabolism	0.268	0.00E+00	0.400	0
K00218	protoporphobilin reductase [EC:1.3.1.33]	Metabolism of Cofactors and Vitamins	0.270	0.00E+00	1.000	2
K08766	carnitine O-palmitoyltransferase 2 [EC:2.3.1.21]	Lipid Metabolism/Endocrine System	0.323	0.00E+00	0.433	2
K03795	sirohdrochlorin cobaltochelatease [EC:4.99.1.3]	Metabolism of Cofactors and Vitamins	0.413	2.70E-07	0.500	2
K01502	aliphatic nitrilase [EC:3.5.5.7]	Xenobiotics Biodegradation and Metabolism	0.436	0.00E+00	1.000	0
K08678	UDP-glucuronate decarboxylase [EC:4.1.1.35]	Carbohydrate Metabolism	0.461	0.00E+00	1.000	2
K01458	N-formylglutamate deformylase [EC:3.5.1.68]	Amino Acid Metabolism/ Carbohydrate Metabolism	0.472	0.00E+00	0.308	0
K05601	hydroxylamine reductase [EC:1.7.99.1]	Energy Metabolism	0.481	0.00E+00	0.696	0
K00836	diaminobutyrate-2-oxoglutarate transaminase [EC:2.6.1.76]	Amino Acid Metabolism	0.481	0.00E+00	0.500	2
K06446	acyl-CoA dehydrogenase [EC:1.3.99.-]	Xenobiotics Biodegradation and Metabolism	0.484	0.00E+00	1.000	1
K10046	GDP-D-mannose 3, 5-epimerase [EC:5.1.3.18 5.1.3.-]	Carbohydrate Metabolism	0.000	0.00E+00	0.500	3
K00808	homoserimidine synthase [EC:2.5.1.44]	Biosynthesis of Other Secondary Metabolites	0.000	0.00E+00	0.500	4
K05826	lysine biosynthesis protein LysW	Amino Acid Metabolism	0.000	0.00E+00	1.000	6
K11160	diacylglycerol O-acyltransferase 2 [EC:2.3.1.20 2.3.1.76]	Lipid Metabolism/ Metabolism of Cofactors and Vitamins	0.000	0.00E+00	0.861	9
K06125	4-hydroxybenzoate hexaprenyltransferase [EC:2.5.1.-]	Metabolism of Cofactors and Vitamins	0.000	0.00E+00	0.238	7
K11433	histone-lysine N-methyltransferase SETMAR [EC:2.1.1.43]	Replication and Repair/ Amino Acid Metabolism	0.000	0.00E+00	0.800	4
K01884	cysteinyl-tRNA synthetase, unknown class [EC:6.1.1.16]	Translation	0.000	0.00E+00	0.410	15
K00725	(N-Acetylneuraminy)-galactosylglucosylceramide	Glycan Biosynthesis and Metabolism	0.032	2.72E-06	0.900	5
K00078	dihydrodiol dehydrogenase / D-xylose 1-dehydrogenase (NADP)	Carbohydrate Metabolism/ Xenobiotics Biodegradation and Metabolism	0.053	0.00E+00	0.333	4
K02319	DNA polymerase I [EC:2.7.7.7]	Replication and Repair/ Nucleotide Metabolism	0.093	1.21E-05	0.774	19
K01574	acetoacetate decarboxylase [EC:4.1.1.4]	Carbohydrate Metabolism/ Lipid Metabolism	0.094	0.00E+00	0.732	7
K00934	arginine kinase [EC:2.7.3.3]	Amino Acid Metabolism	0.216	0.00E+00	0.667	3
K05352	ribitol-5-phosphate 2-dehydrogenase [EC:1.1.1.137]	Carbohydrate Metabolism	0.299	0.00E+00	0.694	7
K00709	histo-blood group ABO system transferase [EC:2.4.1.40 2.4.1.37]	Glycan Biosynthesis and Metabolism	0.311	0.00E+00	1.000	3
K00440	coenzyme F420 hydrogenase alpha subunit [EC:1.12.98.1]	Metabolism of Cofactors and Vitamins	0.392	0.00E+00	1.000	4
K02323	DNA polymerase II small subunit [EC:2.7.7.7]	Replication and Repair/ Nucleotide Metabolism	0.423	1.21E-05	0.774	19
K01655	homocitrate synthase [EC:2.3.3.14]	Amino Acid Metabolism/ Carbohydrate Metabolism	0.427	0.00E+00	0.546	39
K06863	5-formaminoimidazole-4-carboxamide-1-(beta)-D-ribofuranosyl	Nucleotide Metabolism	0.442	2.83E-06	0.476	4
K00019	3-hydroxybutyrate dehydrogenase [EC:1.1.1.30]	Carbohydrate Metabolism/ Lipid Metabolism	0.445	0.00E+00	0.732	7
K02322	DNA polymerase II large subunit [EC:2.7.7.7]	Replication and Repair/ Nucleotide Metabolism	0.454	1.21E-05	0.774	19
K03715	1,2-diacylglycerol 3-beta-galactosyltransferase [EC:2.4.1.46]	Glycan Biosynthesis and Metabolism/ Lipid Metabolism	0.485	0.00E+00	0.250	4
K04566	lysyl-tRNA synthetase, class I [EC:6.1.1.6]	Translation	0.496	0.00E+00	0.600	5
K01762	1-aminocyclopropane-1-carboxylate synthase [EC:4.4.1.14]	Amino Acid Metabolism	0.000	1.94E-03	0.000	1
K03464	mucronolactone D-isomerase [EC:5.3.3.4]	Xenobiotics Biodegradation and Metabolism	0.000	5.00E-03	0.167	2
K03379	cyclohexanone monoxygenase [EC:1.14.13.22]	Xenobiotics Biodegradation and Metabolism	0.000	2.72E-03	0.000	1
K05362	UDP-N-acetylmuramoyl-L-alanyl-D-glutamate-L-lysine ligase	Glycan Biosynthesis and Metabolism	0.000	2.29E-03	0.000	1
K09472	gamma-glutamyl-gamma-aminobutyraldehyde dehydrogenase [EC:1.2.1.-]	Amino Acid Metabolism	0.166	3.26E-03	0.000	1
K08688	creatinease [EC:3.5.3.3]	Amino Acid Metabolism	0.235	1.11E-03	0.145	1
K00938	phosphomevalonate kinase [EC:2.7.4.2]	Biosynthesis of Polyketides and Terpenoids	0.288	1.65E-02	0.000	1
K05858	phospholipase C, beta [EC:3.1.4.11]	Cell Communication/ Signal Transduction/ Neurodegenerative Disease	0.317	4.44E-03	0.067	2
K05929	phosphoethanolamine N-methyltransferase [EC:2.1.1.103]	Lipid Metabolism	0.392	1.34E-03	0.000	1
K00319	methylenetetrahydromethanopterin dehydrogenase [EC:1.5.99.9]	Metabolism of Cofactors and Vitamins	0.410	2.43E-02	0.000	2
K00968	choline-phosphate cytidyltransferase [EC:2.7.7.15]	Lipid Metabolism/ Metabolism of Other Amino Acids	0.424	3.64E-03	0.000	2
K00869	mevalonate kinase [EC:2.7.1.36]	Transport and Catabolism/ Biosynthesis of Polyketides and Terpenoids	0.483	1.64E-02	0.000	1
K00448	protocatechuate 3,4-dioxygenase, alpha subunit [EC:1.13.11.3]	Xenobiotics Biodegradation and Metabolism	0.000	6.86E-04	0.150	4
K00449	protocatechuate 3,4-dioxygenase, beta subunit [EC:1.13.11.3]	Xenobiotics Biodegradation and Metabolism	0.000	6.86E-04	0.150	4
K04100	protocatechuate 4,5-dioxygenase, alpha chain [EC:1.13.11.8]	Xenobiotics Biodegradation and Metabolism	0.000	1.47E-03	0.071	4
K04101	protocatechuate 4,5-dioxygenase, beta chain [EC:1.13.11.8]	Xenobiotics Biodegradation and Metabolism	0.000	1.47E-03	0.071	4
K05549	benzoate 1,2-dioxygenase alpha subunit [EC:1.14.12.10]	Xenobiotics Biodegradation and Metabolism	0.000	6.30E-04	0.000	3
K05784	benzoate 1,2-dioxygenase electron transfer component	Xenobiotics Biodegradation and Metabolism	0.000	6.30E-04	0.000	3
K00446	catechol 2,3-dioxygenase [EC:1.13.11.2]	Xenobiotics Biodegradation and Metabolism	0.000	9.68E-03	0.000	4
K01477	allantoicase [EC:3.5.3.4]	Nucleotide Metabolism	0.000	4.96E-03	0.208	5
K03381	catechol 1,2-dioxygenase [EC:1.13.11.1]	Xenobiotics Biodegradation and Metabolism	0.000	6.56E-03	0.000	5
K00993	ethanolaminephosphotransferase [EC:2.7.8.1]	Lipid Metabolism/ Metabolism of Other Amino Acids	0.069	3.0E-03	0.053	5
K07250	4-aminobutyrate aminotransferase / (S)-3-amino-2-methylpropionate	Amino Acid Metabolism/ Carbohydrate Metabolism/ Metabolism of Other Amino Acids	0.244	1.79E-02	0.183	20
K00276	primary-amine oxidase [EC:1.4.3.21]	Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites	0.279	3.46E-02	0.121	11
K00320	coenzyme F420-dependent N5,N10-methenyltetrahydromethanopterin	Metabolism of Cofactors and Vitamins	0.392	2.33E-02	0.077	5
K00672	formylmethanofuran-tetrahydromethanopterin N-formyltransferase	Energy Metabolism/ Metabolism of Cofactors and Vitamins	0.405	2.66E-02	0.000	17
K00368	nitrile reductase (NO-forming) [EC:1.7.2.1]	Energy Metabolism	0.406	7.78E-05	0.000	12
K01114	phospholipase C [EC:3.1.4.3]	Signaling Molecules and Interaction/ Carbohydrate Metabolism/ Lipid Metabolism	0.424	2.36E-02	0.064	7
K00155	NONE	Biosynthesis of Polyketides and Terpenoids/ Xenobiotics Biodegradation and Metabolism	0.456	3.80E-03	0.167	4
K00804	geranylgeranyl pyrophosphate synthetase [EC:2.5.1.29]	Biosynthesis of Polyketides and Terpenoids	0.479	6.44E-03	0.167	4
K00376	nitrous-oxide reductase [EC:1.7.99.6]	Energy Metabolism	0.499	4.49E-03	0.000	3
K02293	phytoene dehydrogenase, phytoene desaturase [EC:1.14.99.-]	Biosynthesis of Polyketides and Terpenoids	0.000	5.22E-04	0.500	2
K03339	6-phospho-5-dehydro-2-deoxy-D-glucanate aldolase [EC:4.1.2.29]	Carbohydrate Metabolism	0.154	3.33E-03	0.421	1
K11142	cytosol aminopeptidase [EC:3.4.11.1 3.4.11.5]	Amino Acid Metabolism/ Enzyme Families/ Metabolism of Other Amino Acids	0.168	9.70E-04	0.217	1
K01432	arylfomamidase [EC:3.5.1.9]	Amino Acid Metabolism/ Carbohydrate Metabolism	0.216	7.53E-04	0.542	1

K08687	N-carbamoylascosine amidase [EC:3.5.1.59]	Amino Acid Metabolism	0.471	2.22E-03	0.238	2
K00641	homoserine O-acetyltransferase [EC:2.3.1.31]	Amino Acid Metabolism/ Energy Metabolism	0.479	2.11E-03	0.250	2
K06118	UDP-sulfolipoquinovose synthase [EC:3.13.1.1]	Carbohydrate Metabolism/ Lipid Metabolism	0.000	6.27E-04	0.600	4
K02509	2-oxo-hept-3-ene-1,7-diolate hydratase [EC:4.2.1.-]	Amino Acid Metabolism	0.000	5.47E-03	0.333	3
K00802	spermine synthase [EC:2.5.1.22]	Amino Acid Metabolism/ Metabolism of Other Amino Acids	0.000	1.31E-03	0.268	4
K00293	saccharopine dehydrogenase (NADP+, L-glutamate forming)	Amino Acid Metabolism	0.000	1.27E-03	0.600	6
K00295	methylene-tetrahydrofolate dehydrogenase (NAD+) [EC:1.5.1.15]	Metabolism of Cofactors and Vitamins	0.000	5.99E-05	0.667	8
K01907	acetoacetyl-CoA synthetase [EC:6.2.1.16]	Carbohydrate Metabolism/ Lipid Metabolism	0.000	2.79E-04	0.633	8
K11517	(S)-2-hydroxy-acid oxidase [EC:1.1.3.15]	Transport and Catabolism/ Carbohydrate Metabolism	0.000	1.35E-04	0.515	7
K00988	ATP adenyllyltransferase [EC:2.7.7.53]	Nucleotide Metabolism	0.000	1.89E-03	0.276	16
K01769	guanylate cyclase, other [EC:4.6.1.2]	Nucleotide Metabolism	0.000	2.06E-04	0.938	31
K03004	DNA-directed RNA polymerase I subunit A43 [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.000	8.84E-05	0.664	34
K03011	DNA-directed RNA polymerase II subunit C	Replication and Repair/Transcription/ Neurodegenerative Disease	0.000	8.84E-05	0.664	34
K08049	adenylate cyclase 9 [EC:4.6.1.1]	Cell Communication/ Cell Growth and Death/ Signal Transduction	0.000	2.08E-04	0.939	32
K11195	PTS system, fructose-specific IIB component [EC:2.7.1.69]	Membrane Transport/ Carbohydrate Metabolism	0.000	9.91E-04	0.900	5
K00235	succinate dehydrogenase (ubiquinone) iron-sulfur protein	Neurodegenerative Diseases/ Carbohydrate Metabolism/ Energy Metabolism	0.000	3.88E-04	0.612	28
K03053	DNA-directed RNA polymerase subunit H [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.000	8.84E-05	0.664	34
K01511	ectonucleoside triphosphate diphosphohydrolase 5/6 [EC:3.6.1.6]	Nucleotide Metabolism	0.000	1.98E-03	0.377	8
K03918	L-lysine 6-transaminase [EC:2.6.1.36]	Amino Acid Metabolism	0.000	1.18E-02	0.253	8
K00718	galactoside 2-L-fucosyltransferase [EC:2.4.1.69]	Glycan Biosynthesis and Metabolism	0.000	7.50E-03	0.464	8
K07820	beta-1,3-galactosyltransferase 2 [EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	0.000	3.70E-03	0.800	5
K07508	acetyl-CoA acyltransferase 2 [EC:2.3.1.16]	Amino Acid Metabolism/ Lipid Metabolism/ Xenobiotics Biodegradation and Metabolism	0.000	1.85E-02	0.276	39
K00139	succinate-semialdehyde dehydrogenase [EC:1.2.1.24]	Amino Acid Metabolism/ Carbohydrate Metabolism	0.000	2.67E-03	0.609	23
K00894	ethanolamine kinase [EC:2.7.1.82]	Lipid Metabolism	0.000	4.91E-03	0.300	4
K00505	tyrosinase [EC:1.14.18.1]	Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites	0.000	2.23E-03	0.364	12
K00822	beta-alanine-pyruvate transaminase [EC:2.6.1.18]	Amino Acid Metabolism/ Carbohydrate Metabolism/ Metabolism of Other Amino Acids	0.000	4.58E-03	0.300	13
K03416	methylmalonyl-CoA carboxyltransferase [EC:2.1.3.1]	Carbohydrate Metabolism	0.000	8.07E-03	0.460	43
K00143	aminoadipate-semialdehyde dehydrogenase large subunit [EC:1.2.1.31]	Amino Acid Metabolism	0.022	5.48E-03	0.556	7
K00904	deoxyguanosine kinase [EC:2.7.1.113]	Nucleotide Metabolism	0.040	1.37E-04	0.609	11
K03010	DNA-directed RNA polymerase II subunit B [EC:2.7.7.6]	Replication and Repair/Transcription/ Neurodegenerative Disease	0.074	8.84E-05	0.664	34
K10781	fatty acyl-ACP thioesterase B [EC:3.1.2.14 3.1.2.-]	Lipid Metabolism	0.078	7.15E-05	0.768	7
K00392	sulfite reductase (ferredoxin) [EC:1.8.7.1]	Energy Metabolism/ Metabolism of Other Amino Acids	0.082	3.76E-04	0.232	5
K11152	retinol dehydrogenase 11 [EC:1.1.1.-]	Metabolism of Cofactors and Vitamins	0.106	8.39E-04	0.530	8
K00263	leucine dehydrogenase [EC:1.4.1.9]	Amino Acid Metabolism	0.141	1.39E-03	0.212	3
K03021	DNA-directed RNA polymerase III subunit C2 [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism/Immune System	0.149	8.84E-05	0.664	34
K01899	succinyl-CoA synthetase alpha subunit [EC:6.2.1.4 6.2.1.5]	Carbohydrate Metabolism	0.170	2.18E-03	0.491	30
K00886	polyphosphate glucokinase [EC:2.7.1.63]	Carbohydrate Metabolism	0.172	2.23E-03	0.303	23
K07512	mitochondrial trans-2-enoyl-CoA reductase [EC:1.3.1.38]	Lipid Metabolism	0.174	3.71E-03	0.455	7
K01920	glutathione synthase [EC:6.3.2.3]	Metabolism of Other Amino Acids	0.183	6.10E-03	0.238	20
K06208	chorismate mutase [EC:5.4.99.5]	Amino Acid Metabolism	0.195	4.77E-03	0.544	14
K03016	DNA-directed RNA polymerase II subunit H	Replication and Repair/Transcription/ Neurodegenerative Disease	0.208	8.84E-05	0.664	34
K01519	nucleoside-triphosphate pyrophosphatase [EC:3.6.1.19]	Nucleotide Metabolism/ Xenobiotics Biodegradation and Metabolism	0.215	3.08E-03	0.301	52
K01568	pyruvate decarboxylase [EC:4.1.1.1]	Carbohydrate Metabolism	0.221	2.84E-02	0.366	45
K02999	DNA-directed RNA polymerase I subunit A1 [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.255	8.84E-05	0.664	34
K00828	serine-glyoxylate transaminase [EC:2.6.1.45]	Amino Acid Metabolism	0.279	4.12E-03	0.220	24
K00203	formylmethanofuran dehydrogenase subunit D [EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.279	3.39E-03	0.457	27
K00061	retinol dehydrogenase [EC:1.1.1.-]	Metabolism of Cofactors and Vitamins	0.282	4.04E-05	0.433	3
K00125	formate dehydrogenase, beta subunit [EC:1.2.1.2]	Carbohydrate Metabolism/ Energy Metabolism	0.283	4.05E-03	0.247	38
K00114	alcohol dehydrogenase (acceptor) [EC:1.1.99.8]	Carbohydrate Metabolism/ Energy Metabolism/ Xenobiotics Biodegradation and Metabolism	0.291	2.28E-02	0.268	23
K00578	tetrahydromethanopterin S-methyltransferase subunit B [EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.295	1.34E-03	0.364	5
K10251	beta-keto reductase [EC:1.1.1.-]	Lipid Metabolism	0.303	5.24E-03	0.382	13
K00846	ketoheko kinase [EC:2.7.1.3]	Carbohydrate Metabolism	0.317	1.09E-03	0.346	10
K00516	NONE	Xenobiotics Biodegradation and Metabolism	0.322	4.45E-03	0.214	6
K03049	DNA-directed RNA polymerase subunit E [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.327	8.84E-05	0.664	34
K00582	tetrahydromethanopterin S-methyltransferase subunit F [EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.332	1.34E-03	0.364	5
K01573	oxaloacetate decarboxylase, gamma subunit [EC:4.1.1.3]	Amino Acid Metabolism/ Carbohydrate Metabolism	0.336	2.01E-03	0.347	21
K03766	beta-1,3-N-acetylglucosaminyltransferase 5 [EC:2.4.1.206]	Glycan Biosynthesis and Metabolism	0.336	1.64E-02	0.429	7
K00402	methyl-coenzyme M reductase gamma subunit [EC:2.8.4.1]	Metabolism of Cofactors and Vitamins	0.342	7.18E-04	0.242	12
K03047	DNA-directed RNA polymerase subunit D [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.343	8.84E-05	0.664	34
K00552	glycine N-methyltransferase [EC:2.1.1.20]	Amino Acid Metabolism	0.346	5.13E-03	0.325	20
K03044	DNA-directed RNA polymerase subunit B [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.347	8.84E-05	0.664	34
K11473	glycolate oxidase iron-sulfur subunit	Carbohydrate Metabolism	0.348	1.35E-04	0.515	7
K07819	beta-1,3-galactosyltransferase 1 [EC:2.4.1.-]	Glycan Biosynthesis and Metabolism	0.350	3.70E-03	0.800	5
K11204	glutamate-cysteine ligase catalytic subunit [EC:6.3.2.2]	Metabolism of Other Amino Acids	0.352	1.37E-03	0.235	34
K00579	tetrahydromethanopterin S-methyltransferase subunit C [EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.353	1.34E-03	0.364	5
K03042	DNA-directed RNA polymerase subunit A' [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.365	8.84E-05	0.664	34
K03041	DNA-directed RNA polymerase subunit A [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.367	8.84E-05	0.664	34
K00400	methyl coenzyme M reductase system, component A2	Metabolism of Cofactors and Vitamins	0.368	7.18E-04	0.242	12
K01575	acetylacetyl decarboxylase [EC:4.1.1.5]	Carbohydrate Metabolism	0.375	2.09E-03	0.250	3
K00187	2-oxoisovalerate ferredoxin oxidoreductase, beta subunit	Amino Acid Metabolism	0.383	5.63E-04	0.310	4
K00150	glycolaldehyde-3-phosphate dehydrogenase (NAD(P)) [EC:1.2.1.59]	Carbohydrate Metabolism/ Energy Metabolism	0.395	8.67E-04	0.647	14
K00814	alanine transaminase [EC:2.6.1.2]	Amino Acid Metabolism/ Energy Metabolism	0.398	2.66E-03	0.459	37
K02201	panthetheine-phosphate adenyllyltransferase [EC:2.7.7.3]	Metabolism of Cofactors and Vitamins	0.401	7.45E-04	0.278	8
K03045	DNA-directed RNA polymerase subunit B' [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.405	8.84E-05	0.664	34
K00205	formylmethanofuran dehydrogenase subunit F [EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.406	3.39E-03	0.457	27
K04073	acetaldehyde dehydrogenase [EC:1.2.1.10]	Carbohydrate Metabolism	0.407	1.33E-02	0.379	43
K03051	DNA-directed RNA polymerase subunit F [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.409	8.84E-05	0.664	34
K03056	DNA-directed RNA polymerase subunit L [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism	0.411	8.84E-05	0.664	34
K03421	methyl-coenzyme M reductase subunit C	Metabolism of Cofactors and Vitamins	0.413	7.18E-04	0.242	12
K00399	methyl-coenzyme M reductase alpha subunit [EC:2.8.4.1]	Metabolism of Cofactors and Vitamins	0.419	7.18E-04	0.242	12
K00580	tetrahydromethanopterin S-methyltransferase subunit D [EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.425	1.34E-03	0.364	5
K01120	3,5-cyclic-nucleotide phosphodiesterase [EC:3.1.4.17]	Nucleotide Metabolism	0.429	5.54E-03	0.337	5
K00204	formylmethanofuran dehydrogenase subunit H [EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.430	3.39E-03	0.457	27
K08728	nucleoside deoxynibosyltransferase [EC:2.4.2.6]	Nucleotide Metabolism	0.430	1.21E-03	0.589	7
K00581	tetrahydromethanopterin S-methyltransferase subunit E [EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.433	1.34E-03	0.364	5
K01196	amylol-1,6-glucosidase [EC:3.2.1.33]	Carbohydrate Metabolism	0.445	9.05E-03	0.229	20
K10027	phytoene dehydrogenase [EC:1.14.99.-]	Biosynthesis of Polyketides and Terpenoids	0.451	5.23E-04	0.333	3
K00200	formylmethanofuran dehydrogenase subunit A [EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.452	3.39E-03	0.457	27
K03426	NAD+ diphosphatase [EC:3.6.1.22]	Transport and Catabolism/ Metabolism of Cofactors and Vitamins	0.456	4.58E-04	0.576	9
K09011	D-citramalate synthase [EC:2.3.1.182]	Amino Acid Metabolism	0.456	2.44E-03	0.389	60
K00695	sucrose synthase [EC:2.4.1.13]	Carbohydrate Metabolism	0.456	2.58E-04	0.250	4
K05825	2-aminoadipate transaminase [EC:2.6.1.-]	Amino Acid Metabolism	0.463	2.06E-04	0.571	5
K01510	apprase [EC:3.6.1.5]	Signaling Molecules and Interaction/ Nucleotide Metabolism	0.463	1.26E-02	0.266	63
K01922	phosphopantothenate-cysteine ligase [EC:6.3.2.5]	Metabolism of Cofactors and Vitamins	0.465	1.79E-03	0.237	19
K00201	formylmethanofuran dehydrogenase subunit B [EC:1.2.99.5]	Metabolism of Cofactors and Vitamins	0.465	3.39E-03	0.457	27
K02626	arginine decarboxylase [EC:4.1.1.19]	Amino Acid Metabolism	0.470	4.09E-04	0.333	3
K00189	2-oxoisovalerate ferredoxin oxidoreductase, gamma subunit	Amino Acid Metabolism	0.473	5.63E-04	0.310	4
K00577	tetrahydromethanopterin S-methyltransferase subunit A [EC:2.1.1.86]	Metabolism of Cofactors and Vitamins	0.476	1.34E-03	0.364	5
K01490	AMP deaminase [EC:3.5.4.6]	Nucleotide Metabolism	0.478	2.73E-02	0.305	8
K01592	tyrosine decarboxylase [EC:4.1.1.25]	Amino Acid Metabolism/ Biosynthesis of Other Secondary Metabolites	0.482	1.35E-03	0.558	10
K03018	DNA-directed RNA polymerase III subunit C1 [EC:2.7.7.6]	Transcription/ Nucleotide Metabolism/Immune System	0.492	8.84E-05	0.664	34
K00706	1,3-beta-glucan synthase [EC:2.4.1.34]	Carbohydrate Metabolism	0.494	2.14E-03	0.400	4
K00401	methyl-coenzyme M reductase beta subunit [EC:2.8.4.1]	Metabolism of Cofactors and Vitamins	0.499	7.18E-04	0.242	12

**Table S3. Validation of main results**

ANALYSIS	ASSAY 1*	ASSAY 2**	ASSAY 3***
<b>Main Results</b>			
Obesity	1.34E-11	8.93E-06	5.55E-06
IBD	1.94E-09	9.58E-06	4.74E-05
<b>Alternative Dataset</b>			
Twins <sup>#</sup> dataset (Obesity)	9.7E-08	1.6E-04	1.2E-03
<b>Non-Transport Enzymes Analysis</b>			
Omitting transport enzymes (Obesity)	6.59E-10	1.58E-05	3.05E-05
Omitting transport enzymes (IBD)	2.79E-08	3.13E-05	1.61E-04
<b>Robustness to Population Structure</b>			
Danish samples only (Obesity)	2.81E-09	2.50E-05	5.50E-05
Spanish samples only (IBD)	8.94E-10	8.05E-06	1.36E-06
<b>Alternative Enrichment Metrics</b>			
Ranksum (Obesity)	N/A	1.53E-02	1.00E-02
Presence/absence hypergeometric (Obesity)	N/A	3.57E-03	2.18E-03
Difference in rank (Obesity)	N/A	1.28E-03	1.72E-02
Jensen–Shannon divergence (Obesity)	N/A	1.76E-06	1.75E-04
<b>Robustness to Noise in Read Count Data</b>			
Read Threshold = 5 (Obesity)	2.26E-12	6.65E-07	2.46E-07
Read Threshold = 25 (Obesity)	7.47E-09	1.23E-05	8.83E-06
Read Threshold = 50 (Obesity)	3.46E-08	1.30E-06	4.90E-06
Consistently Enriched/Depleted (Obesity)	N/A	2.83E-02	2.44E-02
Read Threshold = 5 (IBD)	2.03E-09	1.20E-05	1.26E-05
Read Threshold = 25 (IBD)	1.18E-06	7.11E-06	6.00E-05
Read Threshold = 50 (IBD)	1.06E-05	1.23E-05	7.68E-05
Consistently Enriched/Depleted (IBD)	N/A	3.09E-02	1.64E-02
<b>Alternative Network Construction Models</b>			
All KEGG Network (Obesity)	4.26E-06	1.25E-03	4.60E-06
Undirected Edges (Obesity)	2.53E-06	1.12E-03	2.66E-03
Omitting Currency Metabolites (Obesity)	2.07E-09	9.62E-04	8.35E-04
SEED-based Network (Obesity)	6.04E-03	3.48E-02	1.13E-02
All KEGG Network (IBD)	1.35E-04	6.80E-03	1.95E-03
Undirected Edges (IBD)	7.67E-05	8.59E-03	7.69E-03
Omitting Currency Metabolites (IBD)	2.22E-07	7.67E-05	1.70E-03
SEED-based Network (IBD)	1.30E-03	1.10E-03	1.89E-03

Three assays are used to validate the association between enzyme centrality and differential abundance under a number of different conditions, specified in the table above. See Supporting Text for more details.

\*Assay 1: p-value of the Spearman correlation between centrality and differential abundance score

\*\*Assay 2: p-value of the Wilcoxon ranksum test comparing the centrality of host-state associated enzymes to the centrality of other enzymes

\*\*\*Assay 3: p-value of the Hypergeometric enrichment test measuring over-representation of host-state associated enzymes in the peripheral tier of the network

<sup>#</sup>Turnbaugh PJ et al. (2009) A core gut microbiome in obese and lean twins. Nature 457:480-4.

**Table S4. Functional enrichment of host-state associated enzymes according to KEGG BRITE classes**

Centrality Class	Association Class	Over-Represented Functions	Under-Represented Functions
All Enzymes	Obese-Depleted	Cell Communication**	Membrane Transport**
		Replication and Repair**	Amino Acid Metabolism *
		Transcription***	Carbohydrate Metabolism ***
		Neurodegenerative Diseases***	Biosynthesis of Polyketides and Terpenoids*
		Metabolism of Cofactors and Vitamins*	Energy Metabolism*
		Nucleotide Metabolism**	
		Circulatory System*	
		Immune System**	
	Obese- Enriched	Membrane Transport*	Transcription*
			Glycan Biosynthesis and Metabolism*
	IBD-Depleted	Cell Communication**	Membrane Transport**
		Transcription***	Carbohydrate Metabolism ***
		Neurodegenerative Diseases**	Energy Metabolism**
		Nucleotide Metabolism*	
		Circulatory System*	
		Immune System*	
	IBD-Enriched	Membrane Transport*	Metabolism of Cofactors and Vitamins*
			Nucleotide Metabolism*
			Replication and Repair*
			Transcription*
Peripheral Enzymes	Obese-Depleted	Transcription***	Carbohydrate Metabolism***
		Nucleotide Metabolism***	Amino Acid Metabolism**
		Signal Transduction*	Membrane Transport*
		Replication and Repair***	Energy Metabolism*
		Neurodegenerative Diseases**	
		Immune System *	
	Obese- Enriched	Membrane Transport***	Metabolism of Cofactors and Vitamins*
	IBD-Depleted	Replication and Repair**	Amino Acid Metabolism**
		Transcription***	Carbohydrate Metabolism*
		Neurodegenerative Diseases*	Energy Metabolism**
		Nucleotide Metabolism***	Metabolism of Cofactors and Vitamins*
	IBD-Enriched	Membrane Transport***	
	All Enzymes	Membrane Transport***	Amino Acid Metabolism***
		Replication and Repair***	Carbohydrate Metabolism***
		Translation***	Energy Metabolism*
		Transcription***	Endocrine System*
		Nucleotide Metabolism**	Metabolism of Cofactors and Vitamins*

Functional classes that are significantly over- or under-represented among enzymes in the specified classes compared to all enzymes in the metabolic network, according to a Hypergeometric enrichment test. \* p<0.05, \*\* p<.005, \*\*\* p<0.0005

**Table S5. 326 reference genomes used for single genome analysis**

Abiotrophia_defectiva_ATCC_49176	Coprococcus_eutactus_ATCC_27759	Lactobacillus_reuteri_JCM_1112
Acidaminococcus_sp_D21	Corynebacterium_accolens_ATCC_49725	Lactobacillus_reuteri_MM2-3
Acinetobacter_calcoaceticus_RUH2202	Corynebacterium_amycolatum_SK46	Lactobacillus_reuteri_MM4-1
Acinetobacter_johnsonii_SH046	Corynebacterium_aurimucosum_ATCC_700975	Lactobacillus_reuteri_SD2112
Acinetobacter_junii_SH205	Corynebacterium_efficiens_YS-314	Lactobacillus_rhamnosus_LMS2-1
Acinetobacter_lwoffii_SH145	Corynebacterium_genitalium_ATCC_33030	Lactobacillus_ruminis_ATCC_25644
Acinetobacter_radioresistens_SH164	Corynebacterium_glucuronolyticum_ATCC_51866	Lactobacillus_sakei_subsp._carnosus_DSM_15831
Acinetobacter_radioresistens_SK82	Corynebacterium_glucuronolyticum_ATCC_51867	Lactobacillus_sakei_subsp._sakei_23K
Acinetobacter_sp._ATCC_27244	Corynebacterium_lipophiloflavum_DSM_44291	Lactobacillus_salivarius_ATCC_11741
Actinobacillus_pleuropneumoniae_L20	Corynebacterium_matruchotii_ATCC_14266	Lactobacillus_salivarius_UCC118
Actinomyces_colecanis_DSM_15436	Corynebacterium_matruchotii_ATCC_33806	Lactobacillus_ultunensis_DSM_16047
Actinomyces_odontolyticus_ATCC_17982	Corynebacterium_pseudogenitalium_ATCC_33035	Lactobacillus_vaginalis_ATCC_49540
Actinomyces_sp._oral_taxon_848_str._F0332	Corynebacterium_striatum_ATCC_6940	Lactococcus_lactis_subsp._lactis_II1403
Actinomyces_urogenitalis_DSM_15434	Corynebacterium_tuberculostearicum_SK141	Leptotrichia_hofstadii_F0254
Aeromicrobium_marinum_DSM_15272	Cronobacter_sakazakii_ATCC_BAA-894	Leuconostoc_mesenteroides_subsp._cremoris_ATCC_19254
Akkermansia_muciniphila_ATCC_BAA-835	Desulfovibrio_piger_ATCC_29098	Listeria_grayi_DSM_20601
Alistipes_putredinis_DSM_17216	Desulfovibrio_vulgaris_subsp._vulgaris_str._Hildenbrough	Methanobrevibacter_smithii_ATCC_35061
Anaerococcus_hydrogenalis_DSM_7454	Dialister_invisus_DSM_15470	Methanobrevibacter_smithii_DSM_2374
Anaerococcus_lactolyticus_ATCC_51172	Dorea_formicigenerans_ATCC_27755	Methanobrevibacter_smithii_DSM_2375
Anaerococcus_tetradius_ATCC_35098	Dorea_longicatena_DSM_13814	Methanosphaera_stadtmanae_DSM_3091
Anaerococcus_vaginalis_ATCC_51170	Eikenella_corrodens_ATCC_23834	Mitsuokella_multacida_DSM_20544
Anaerofustis_stercorihominis_DSM_17244	Enhydrobacter_aerosaccus_SK60	Mobiluncus_curtisii_ATCC_43063
Anaerostipes_caccae_DSM_14662	Enterobacter_cancerogenus_ATCC_35316	Mobiluncus_mulieris_ATCC_35243
Anaerotruncus_colihominis_DSM_17241	Enterobacter_sp._638	Mollicutes_bacterium_D7
Atopobium_rimae_ATCC_49626	Enterococcus_faecalis_ATCC_29200	Neisseria_cinerea_ATCC_14685
Atopobium_vaginae_DSM_15829	Enterococcus_faecalis_HH22	Neisseria_flavescens_NRL30031-H210
Bacteroides_caccae_ATCC_43185	Enterococcus_faecalis_TUSoD_Ef11	Neisseria_flavescens_SK114
Bacteroides_capillosus_ATCC_29799	Enterococcus_faecalis_TX0104	Neisseria_lactamica_ATCC_23970
Bacteroides_cellulosilyticus_DSM_14838	Enterococcus_faecalis_TX1332	Neisseria_mucosa_ATCC_25996
Bacteroides_coprocola_DSM_17136	Enterococcus_faecium_DO	Neisseria_sicca_ATCC_29256
Bacteroides_coprophilus_DSM_18228	Enterococcus_faecium_TX1330	Neisseria_subflava_NJ9703
Bacteroides_dorei_DSM_17855	Erysipelothrix_rhusiopathiae_ATCC_19414	Oribacterium_sinus_F0268
Bacteroides_eggerthii_DSM_20697	Escherichia_coli_83972	Oxalobacter_formigenes_HOxBSL
Bacteroides_finegoldii_DSM_17565	Escherichia_coli_O157-H7_str.EC4115	Oxalobacter_formigenes_OXCC13
Bacteroides_fragilis_3_1_12	Escherichia_coli_SE11	Parabacteroides_distasonis_ATCC_8503
Bacteroides_intestinalis_DSM_17393	Escherichia_coli_UT189	Parabacteroides_johnsonii_DSM_18315
Bacteroides_ovatus_ATCC_8483	Escherichia_coli_str_K_12_substr_MG1655	Parabacteroides_merdae_ATCC_43184
Bacteroides_pectinophilus_ATCC_43243	Escherichia_fergusonii_ATCC_35469	Pasteurella_multocida_subsp._multocida_str._Pm70
Bacteroides_plebeius_DSM_17135	Escherichia_sp._1_1_43	Pediococcus_pentosaceus_ATCC_25745
Bacteroides_sp._1_1_6	Escherichia_sp._3_2_53FAA	Peptostreptococcus_micros_ATCC_33270
Bacteroides_sp._2_1_7	Escherichia_sp._4_1_40B	Porphyromonas_endodontalis_ATCC_35406
Bacteroides_sp._2_2_4	Eubacterium_biforme_DSM_3989	Porphyromonas_gingivalis_ATCC_33277
Bacteroides_sp._3_2_5	Eubacterium_dolichum_DSM_3991	Porphyromonas_uenonis_60-3
Bacteroides_sp._4_3_47FAA	Eubacterium_hallii_DSM_3353	Prevotella_bergensis_DSM_17361
Bacteroides_sp._9_1_42FAA	Eubacterium_rectale_ATCC_33656	Prevotella_copri_DSM_18205
Bacteroides_sp._D1	Eubacterium_saphenum_ATCC_49989	Prevotella_melaninogenica_ATCC_25845
Bacteroides_sp._D2	Eubacterium_siraeum_DSM_15702	Prevotella_oris_F0302
Bacteroides_sp._D4	Eubacterium_ventriosum_ATCC_27560	Prevotella_tanneriae_ATCC_51259
Bacteroides_stercoris_ATCC_43183	Faecalibacterium_prausnitzii_A2-165	Prevotella_veroralis_F0319
Bacteroides_thetaiotaomicron_VPI-5482	Faecalibacterium_prausnitzii_M21-2	Propionibacterium_acnes_SK137
Bacteroides_uniformis_ATCC_8492	Finegoldia_magna_ATCC_29328	Propionibacterium_sp._oral_taxon_191_str._F0233
Bacteroides_vulgatus_ATCC_8482	Finegoldia_magna_ATCC_53516	Proteus_mirabilis_ATCC_29906
Bifidobacterium_adolescentis_L2-32	Fusobacterium_gonidiaformans_ATCC_25563	Proteus_mirabilis_HI4320
Bifidobacterium_angulatum_DSM_20098	Fusobacterium_mortiferum_ATCC_9817	Proteus_penneri_ATCC_35198
Bifidobacterium_animalis_subsp._lactis_AD011	Fusobacterium_nucleatum_subsp._nucleatum_ATCC_25586	Providencia_alcalifaciens_DSM_30120
Bifidobacterium_bifidum_NCIMB_41171	Fusobacterium_periodonticum_ATCC_33693	Providencia_retti_DSM_1131
Bifidobacterium_breve_DSM_20213	Fusobacterium_sp._2_1_31	Providencia_rustigianii_DSM_4541
Bifidobacterium_catenulatum_DSM_16992	Fusobacterium_sp._3_1_5R	Providencia_stuartii_ATCC_25827
Bifidobacterium_dentium_ATCC_27678	Fusobacterium_sp._4_1_13	Pseudomonas_aeruginosa_LESB58
Bifidobacterium_dentium_Bd1	Fusobacterium_sp._7_1	Rhodococcus_erythropolis_SK121

Bifidobacterium_gallicum_DSM_20093	Fusobacterium_sp._D11	Roseburia_intestinalis_L1-82
Bifidobacterium_longum_subsp._infantis_ATCC_55813	Gemella_haemolysans_ATCC_10379	Roseburia_inulinivorans_DSM_16841
Bifidobacterium_longum_subsp._infantis_CCUG_52486	Granulicatella_adiacens_ATCC_49175	Rothia_mucilaginosa_ATCC_25296
Bifidobacterium_pseudocatenulatum_DSM_20438	Haemophilus_influenzae_3655	Ruminococcus_gnavus_ATCC_29149
Blautia_hansenii_DSM_20583	Haemophilus_influenzae_86-028NP	Ruminococcus_lactaris_ATCC_29176
Blautia_hydrogenotrophica_DSM_10507	Haemophilus_parasuis_29755	Ruminococcus_obeum_ATCC_29174
Bryantella_formatexigens_DSM_14469	Haemophilus_parasuis_SH0165	Ruminococcus_sp._5_1_39BFAA
Butyrivibrio_crossotus_DSM_2876	Helicobacter_bilis_ATCC_43879	Ruminococcus_torques_ATCC_27756
Campylobacter_conciscus_13826	Helicobacter_canadensis_MIT_98-5491	Salmonella_enterica_subsp._enterica_serovar_Agona_str._SL483
Campylobacter_gracilis_RM3268	Helicobacter_cinaedi_CCUG_18818	Selenomonas_flueggei_ATCC_43531
Campylobacter_hominis_ATCC_BAA_381	Helicobacter_pullorum_MIT_98-5489	Selenomonas_noxia_ATCC_43541
Campylobacter_rectus_RM3267	Helicobacter_pullorum_MIT_98_5489	Selenomonas_sputigena_ATCC_35185
Campylobacter_showae_RM3277	Helicobacter_pylori_26695	Shigella_sp._D9
Candidatus_Sulcia_muelleri_GWSS	Helicobacter_winghamensis_ATCC_BAA-430	Shuttleworthia_satelles_DSM_14600
Capnocytophaga_gingivalis_JCVIHP016	Holdemania_filiformis_DSM_12042	Slackia_exigua_ATCC_700122
Capnocytophaga_sputigena_Capno	Jonquetella_anthropi_E3_33_E1	Sphingobacterium_spiritivorum_ATCC_33300
Cardiobacterium_hominis_ATCC_15826	Kingella_oralis_ATCC_51147	Sphingobacterium_spiritivorum_ATCC_33861
Catenibacterium_mitsuokai_DSM_15897	Klebsiella_pneumoniae_342	Staphylococcus_aureus_subsp._aureus_MN8
Catonella_morbi_ATCC_51271	Lactobacillus_acidophilus_ATCC_4796	Staphylococcus_aureus_subsp._aureus_TCH130
Chryseobacterium_gleum_ATCC_35910	Lactobacillus_acidophilus_NCFM	Staphylococcus_aureus_subsp._aureus_TCH60
Citrobacter_koseri_ATCC_BAA-895	Lactobacillus_antri_DSM_16041	Staphylococcus_aureus_subsp._aureus_TCH70
Citrobacter_sp._30_2	Lactobacillus_buchneri_ATCC_11577	Staphylococcus_aureus_subsp._aureus_USA300_TCH1516
Citrobacter_youngae_ATCC_29220	Lactobacillus_casei_ATCC_334	Staphylococcus_aureus_subsp._aureus_USA300_TCH959
Clostridiales_bacterium_1_7_47_FAA	Lactobacillus_coleohominis_101-4-CHN	Staphylococcus_capitis_SK14
Clostridium_asparagiforme_DSM_15981	Lactobacillus_crispatus_JV-V01	Staphylococcus_epidermidis_BCM-HMP0060
Clostridium_bartlettii_DSM_16795	Lactobacillus_crispatus_MV-1A-US	Staphylococcus_epidermidis_M23864-W1
Clostridium_bolteae_ATCC_BAA-613	Lactobacillus_delbrueckii_subsp._bulgaricus_ATCC_11842	Staphylococcus_epidermidis_W23144
Clostridium_difficile_630	Lactobacillus_fermentum_ATCC_14931	Staphylococcus_hominis_SK119
Clostridium_hathewayi_DSM_13479	Lactobacillus_fermentum_IFO_3956	Staphylococcus_saprophyticus_subsp._saprophyticus_ATCC_C_15305
Clostridium_hiranois_DSM_13275	Lactobacillus_gasseri_202-4	Staphylococcus_warneri_L37603
Clostridium_hylemonae_DSM_15053	Lactobacillus_gasseri_ATCC_33323	Streptococcus_gordonii_str._Challis_substr._CH1
Clostridium_leptum_DSM_753	Lactobacillus_gasseri_JV-V03	Streptococcus_infantarius_subsp._infantarius_ATCC_BAA-102
Clostridium_methylpentosum_DSM_5476	Lactobacillus_gasseri_MV-22	Streptococcus_mutans_UA159
Clostridium_nexile_DSM_1787	Lactobacillus_helveticus_DPC_4571	Streptococcus_pneumoniae
Clostridium_perfringens_ATCC_13124	Lactobacillus_helveticus_DSM_20075	Streptococcus_pneumoniae_TCH8431-19A
Clostridium_phytofermentans_ISDg	Lactobacillus_hilgardii_ATCC_8290	Streptococcus_pyogenes_M1_GAS
Clostridium_amosum_DSM_1402	Lactobacillus_iners_DSM_13335	Streptococcus_salivarius_SK126
Clostridium_scindens_ATCC_35704	Lactobacillus_jensenii_1153	Streptococcus_sanguinis_SK36
Clostridium_sp._7_2_43FAA	Lactobacillus_jensenii_269-3	Streptococcus_suis_SC84
Clostridium_sp._L2-50	Lactobacillus_jensenii_27-2-CHN	Streptococcus_thermophilus_LMD-9
Clostridium_sp._M62-1	Lactobacillus_jensenii_JV-V16	Subdoligranulum_variabile_DSM_15176
Clostridium_sp._SS2-1	Lactobacillus_johnsonii	Thermoanaerobacter_sp._X514
Clostridium_spiroforme_DSM_1552	Lactobacillus_johnsonii_ATCC_33200	Treponema_vincentii_ATCC_35580
Clostridium_sporogenes_ATCC_15579	Lactobacillus_johnsonii_NCC_533	Tropheryma_whipplei_TW08-27
Collinsella_aerofaciens_ATCC_25986	Lactobacillus_paracasei_subsp._paracasei_8700-2	Veillonella_dispar_ATCC_17748
Collinsella_intestinalis_DSM_13280	Lactobacillus_paracasei_subsp._paracasei_ATCC_25302	Weissella_paramesenteroides_ATCC_33313
Collinsella_stercoris_DSM_13279	Lactobacillus_plantarum_subsp._plantarum_ATCC_14917	
Coprococcus_comes_ATCC_27758	Lactobacillus_reuteri_CF48-3A	